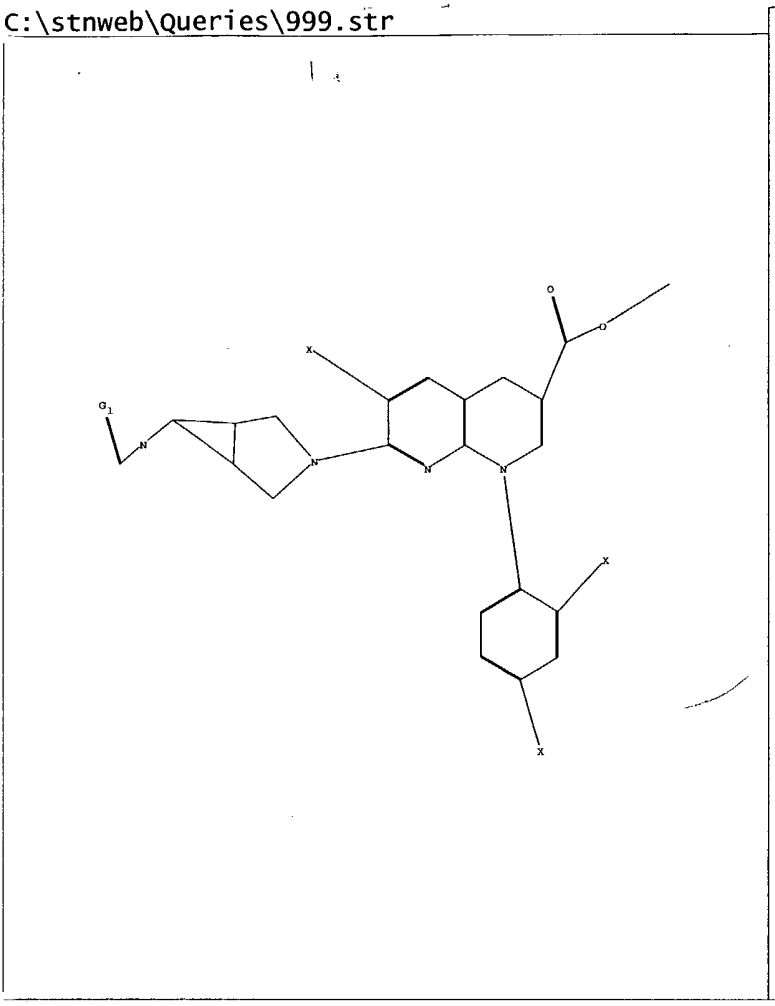
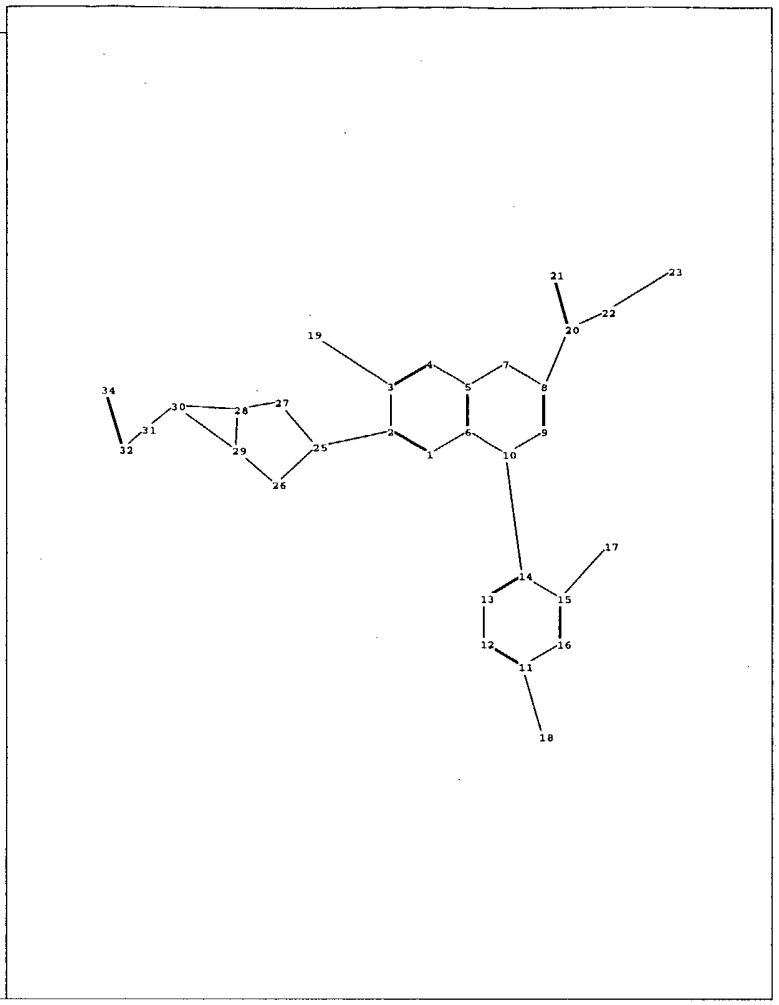
C:\stnweb\Queries\999.str



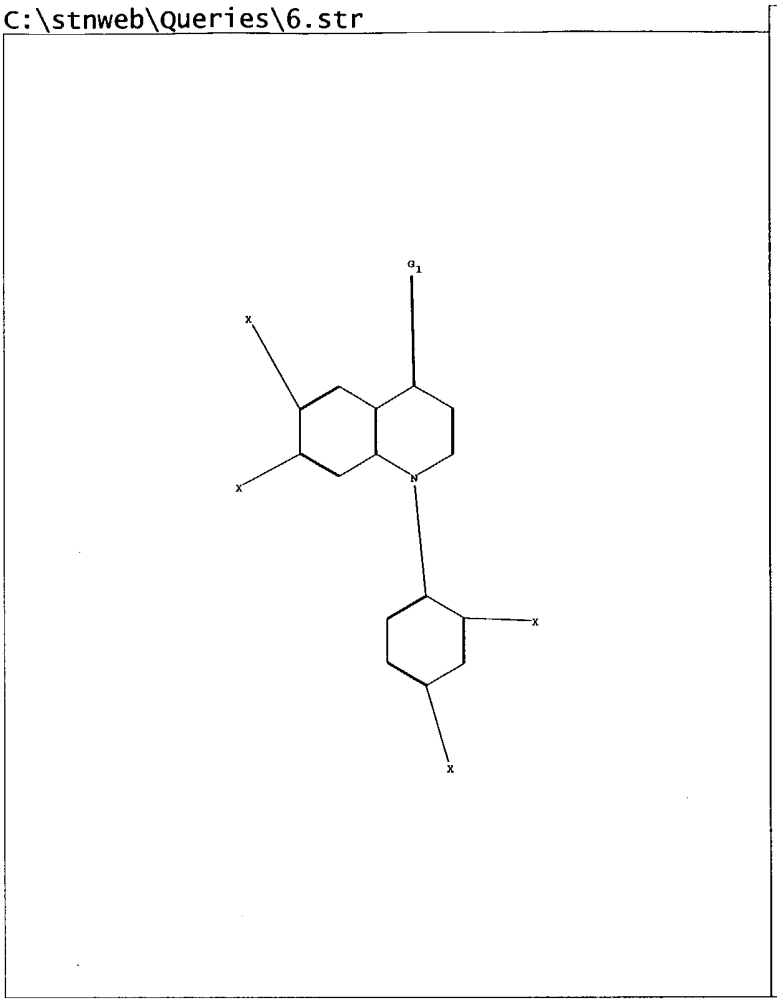


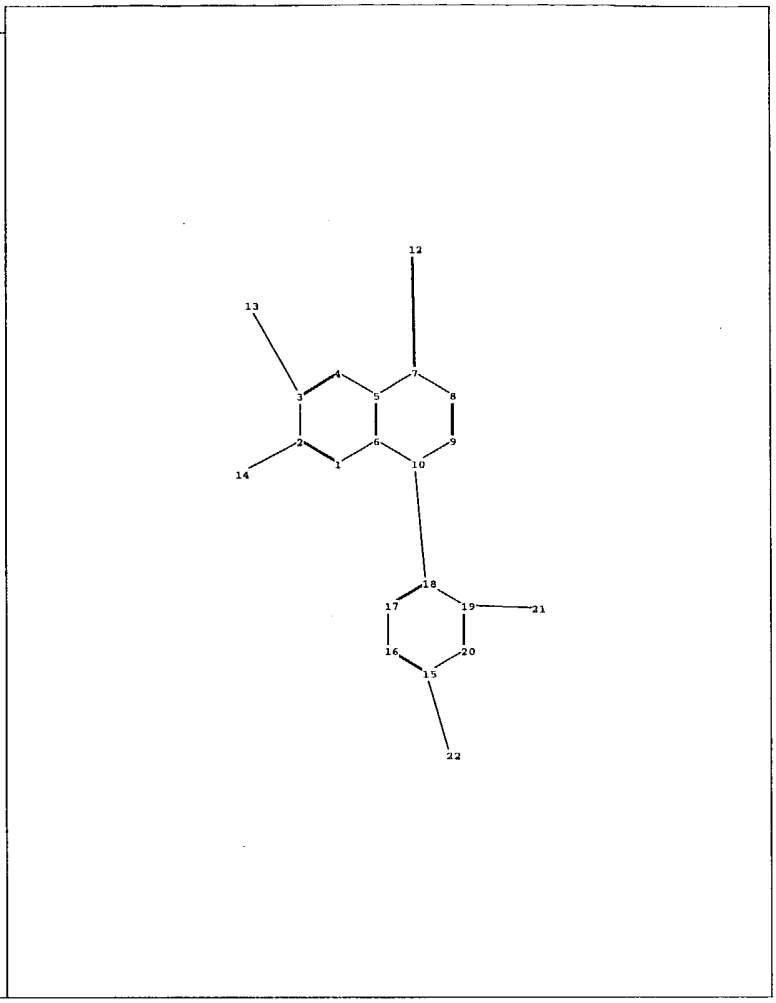
chain nodes :
17 18 19 20 21 22 31 32 34
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 25 26 27 28 29 30
ring/chain nodes :
23
chain bonds :
2-25 3-19 8-20 10-14 11-18 15-17 20-21 20-22 22-23 30-31 31-32 32-34
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14 14-15
15-16 25-26 25-27 26-29 27-28 28-29 28-30 29-30
exact/norm bonds :
2-25 5-7 6-10 7-8 8-9 9-10 10-14 20-21 20-22 22-23 25-26 25-27 26-29 27-28
28-29 28-30 29-30 30-31 31-32 32-34
exact bonds :
3-19 8-20 11-18 15-17
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16
isolated ring systems :
containing 1 : 11 : 25 :

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS 20:CLASS
21:CLASS 22:CLASS 23:CLASS 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom
31:CLASS 32:CLASS 34:CLASS

C:\stnweb\Queries\6.str



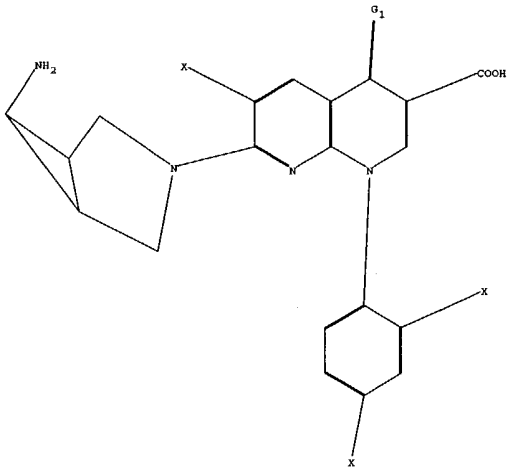



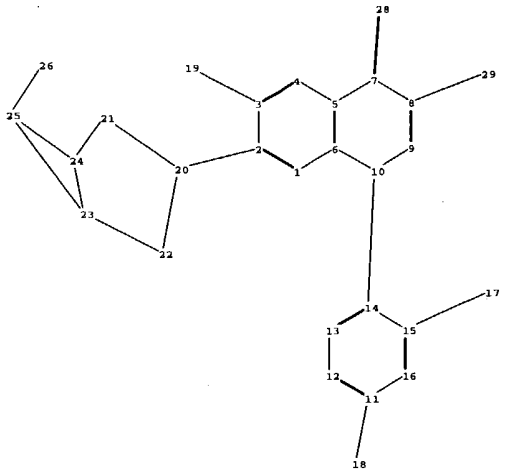

chain nodes :
12 13 14 21 22
ring nodes :
1 2 3 4 5 6 7 8 9 10 15 16 17 18 19 20
chain bonds :
2-14 3-13 7-12 10-18 15-22 19-21
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 15-16 15-20 16-17 17-18 18-19
19-20
exact/norm bonds :
5-7 6-10 7-8 7-12 8-9 9-10 10-18
exact bonds :
2-14 3-13 15-22 19-21
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 15-16 15-20 16-17 17-18 18-19 19-20
isolated ring systems :
containing 1 : 15 :

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 12:CLASS
13:CLASS 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom 21:CLASS
22:CLASS

C:\stnweb\Queries\98.str



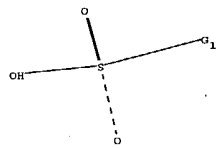



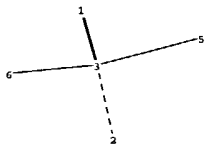

chain nodes :
17 18 19 26 28 29
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 20 21 22 23 24 25
chain bonds :
2-20 3-19 7-28 8-29 10-14 11-18 15-17 25-26
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14 14-15
15-16 20-21 20-22 21-24 22-23 23-24 23-25 24-25
exact/norm bonds :
2-20 5-7 6-10 7-8 7-28 8-9 9-10 10-14 20-21 20-22 21-24 22-23 23-24 23-25
24-25 25-26
exact bonds :
3-19 8-29 11-18 15-17
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16
isolated ring systems :
containing 1 : 11 :

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:CLASS 28:CLASS 29:CLASS

C:\stnweb\Queries\5.str



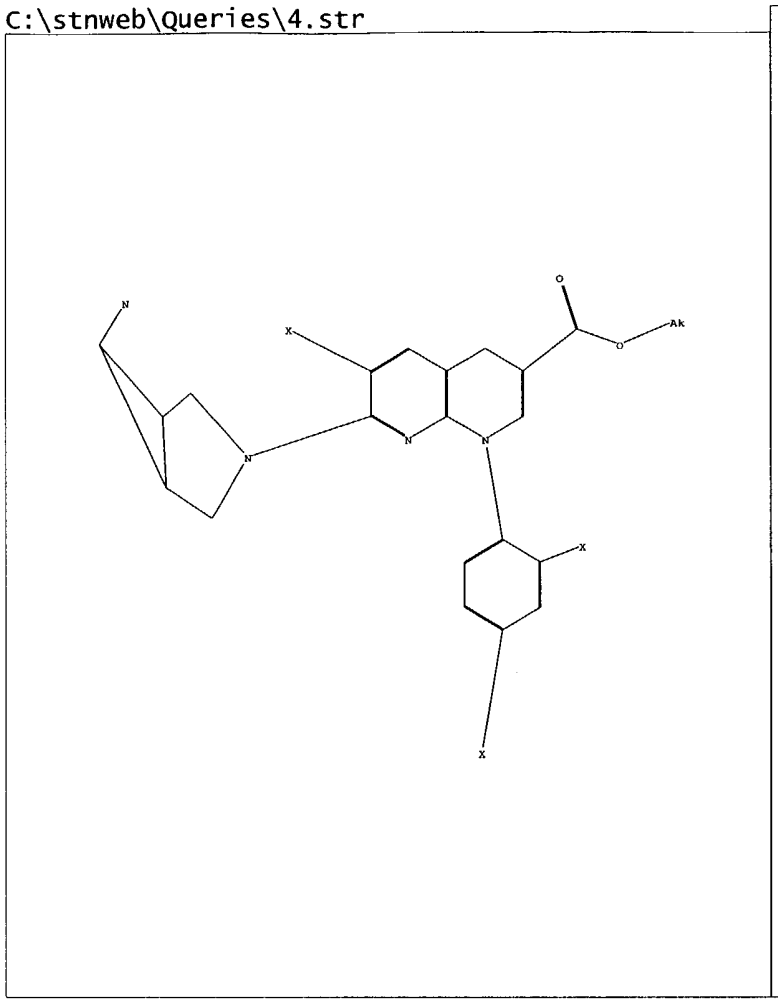



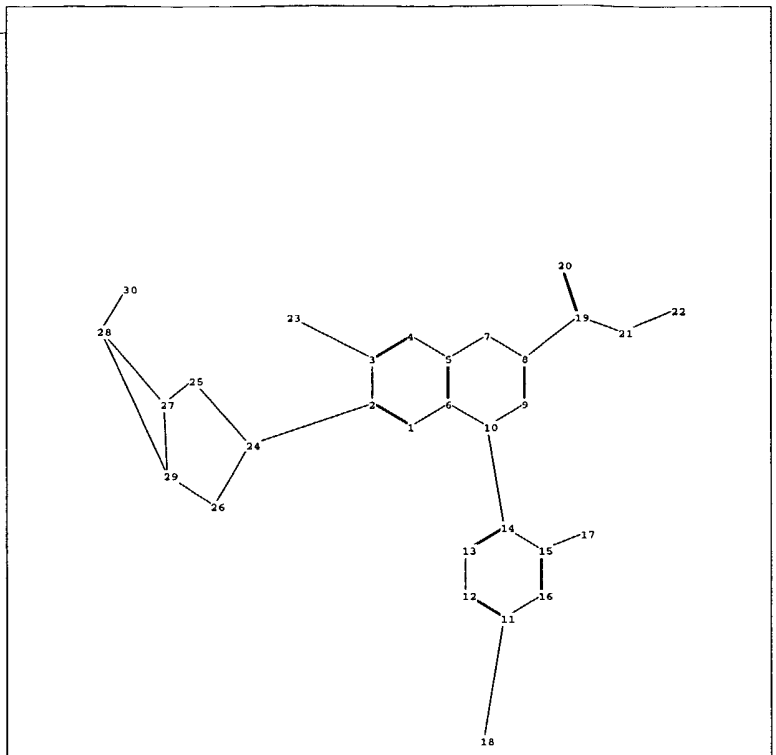

chain nodes :
1 2 3 5 6
chain bonds :
1-3 2-3 3-5 3-6
exact/norm bonds :
2-3 3-5
normalized bonds :
1-3 3-6

G1:CH3,Et

Match level :
1:CLASS 2:CLASS 3:CLASS 5:CLASS 6:CLASS

C:\stnweb\Queries\4.str

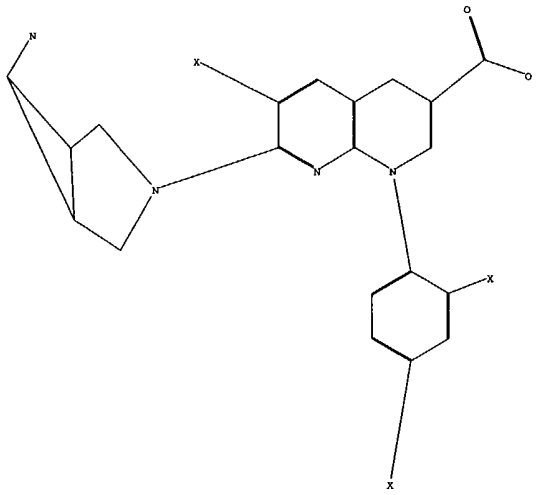


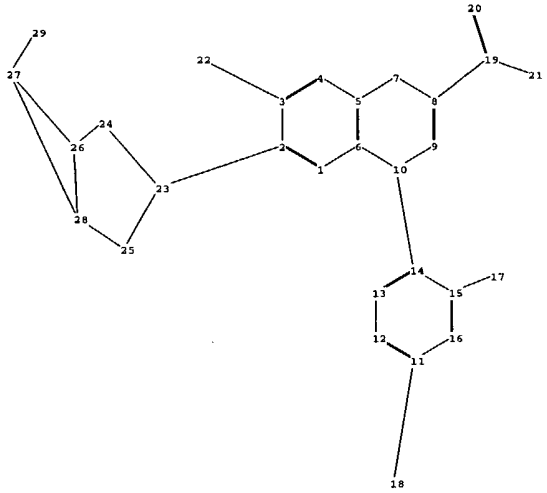




chain nodes :
17 18 19 20 21 22 23 30
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 24 25 26 27 28 29
chain bonds :
2-24 3-23 8-19 10-14 11-18 15-17 19-20 19-21 21-22 28-30
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14 14-15
15-16 24-25 24-26 25-27 26-29 27-28 27-29 28-29
exact/norm bonds :
2-24 5-7 6-10 7-8 8-9 9-10 10-14 19-20 19-21 21-22 24-25 24-26 25-27 26-29
27-28 27-29 28-29 28-30
exact bonds :
3-23 8-19 11-18 15-17
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS 20:CLASS
21:CLASS 22:CLASS 23:CLASS 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom
30:CLASS

C:\stnweb\Queries\8.str

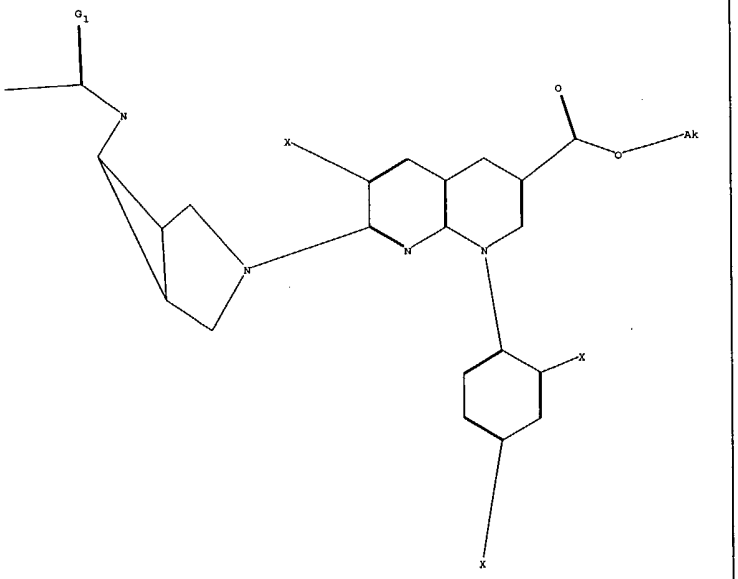


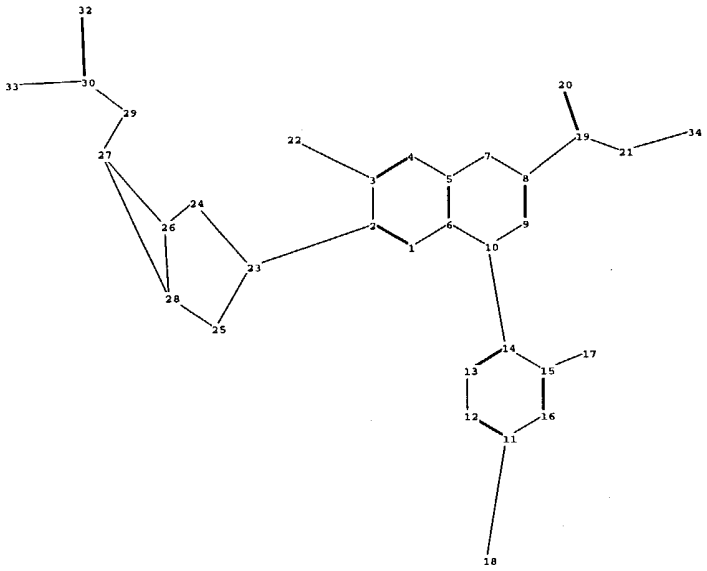




chain nodes :
17 18 19 20 21 22 29
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 23 24 25 26 27 28
chain bonds :
2-23 3-22 8-19 10-14 11-18 15-17 19-20 19-21 27-29
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14 14-15
15-16 23-24 23-25 24-26 25-28 26-27 26-28 27-28
exact/norm bonds :
2-23 5-7 6-10 7-8 8-9 9-10 10-14 19-20 19-21 23-24 23-25 24-26 25-28 26-27
26-28 27-28 27-29
exact bonds :
3-22 8-19 11-18 15-17
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS 20:CLASS
21:CLASS 22:CLASS 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:CLASS

C:\stnweb\Queries\64.str




chain nodes :
17 18 19 20 21 22 29 30 32 34
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 23 24 25 26 27 28
ring/chain nodes :
33
chain bonds :
2-23 3-22 8-19 10-14 11-18 15-17 19-20 19-21 21-34 27-29 29-30 30-32 30-33
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14 14-15
15-16 23-24 23-25 24-26 25-28 26-27 26-28 27-28
exact/norm bonds :
2-23 5-7 6-10 7-8 8-9 9-10 10-14 19-20 19-21 21-34 23-24 23-25 24-26 25-28
26-27 26-28 27-28 27-29 29-30 30-32
exact bonds :
3-22 8-19 11-18 15-17 30-33
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS 20:CLASS
21:CLASS 22:CLASS 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:CLASS
30:CLASS 32:CLASS 33:CLASS 34:CLASS

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

| | | |
|---|---|---|
| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
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| NEWS 3 | SEP 09 | CA/CAplus records now contain indexing from 1907 to the present |
| NEWS 4 | DEC 08 | INPADOC: Legal Status data reloaded |
| NEWS 5 | SEP 29 | DISSABS now available on STN |
| NEWS 6 | OCT 10 | PCTFULL: Two new display fields added |
| NEWS 7 | OCT 21 | BIOSIS file reloaded and enhanced |
| NEWS 8 | OCT 28 | BIOSIS file segment of TOXCENTER reloaded and enhanced |
| NEWS 9 | NOV 24 | MSDS-CCOHS file reloaded |
| NEWS 10 | DEC 08 | CABA reloaded with left truncation |
| NEWS 11 | DEC 08 | IMS file names changed |
| NEWS 12 | DEC 09 | Experimental property data collected by CAS now available in REGISTRY |
| NEWS 13 | DEC 09 | STN Entry Date available for display in REGISTRY and CA/CAplus |
| NEWS 14 | DEC 17 | DGENE: Two new display fields added |
| NEWS 15 | DEC 18 | BIOTECHNO no longer updated |
| NEWS 16 | DEC 19 | CROPU no longer updated; subscriber discount no longer available |
| NEWS 17 | DEC 22 | Additional INPI reactions and pre-1907 documents added to CAS databases |
| NEWS 18 | DEC 22 | IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields |
| NEWS 19 | DEC 22 | ABI-INFORM now available on STN |
| NEWS 20 | JAN 27 | Source of Registration (SR) information in REGISTRY updated and searchable |
| NEWS 21 | JAN 27 | A new search aid, the Company Name Thesaurus, available in CA/CAplus |
| NEWS 22 | FEB 05 | German (DE) application and patent publication number format changes |
| NEWS 23 | MAR 03 | MEDLINE and LMEDLINE reloaded |
| NEWS 24 | MAR 03 | MEDLINE file segment of TOXCENTER reloaded |
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| NEWS 28 | MAR 29 | No connect hour charges in WPIFV until May 1, 2004 |
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| | |
|---|---|
| NEWS EXPRESS | MARCH 5 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004 |
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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004

```
=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
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STRUCTURE FILE UPDATES:   29 MAR 2004  HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES:  29 MAR 2004  HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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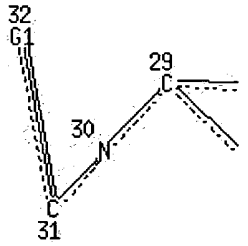
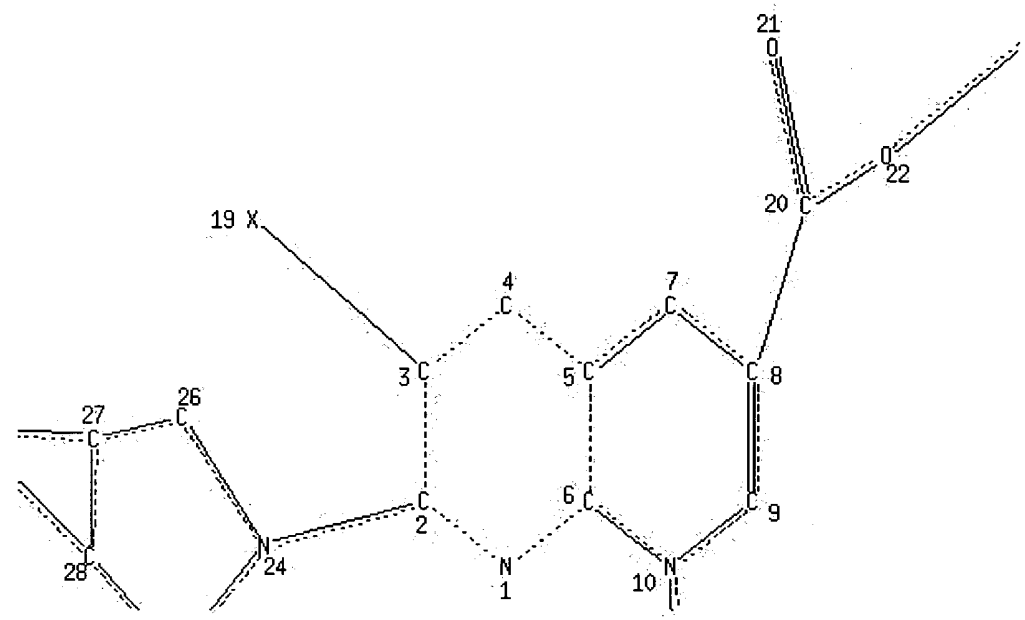
L1       STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1                STR
 0 33 S 34
```

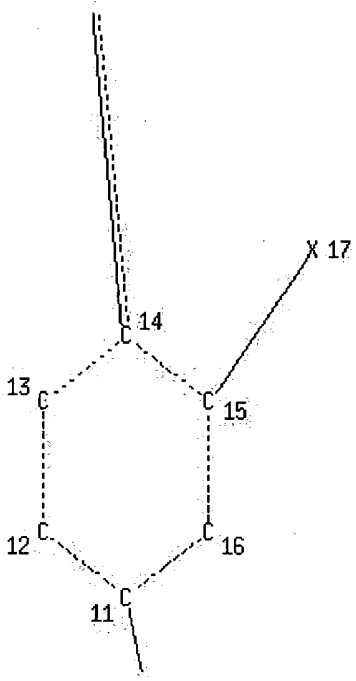



Page 1-A




Page 1-B


Page 1-C


Page 2-B


Page 3-B
VAR G1=33/34
NODE ATTRIBUTES:
NSPEC IS R AT 1

```
NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
NSPEC   IS R      AT   4
NSPEC   IS R      AT   5
NSPEC   IS R      AT   6
NSPEC   IS R      AT   7
NSPEC   IS R      AT   8
NSPEC   IS R      AT   9
NSPEC   IS R      AT  10
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
NSPEC   IS R      AT  14
NSPEC   IS R      AT  15
NSPEC   IS R      AT  16
NSPEC   IS C      AT  17
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
NSPEC   IS C      AT  21
NSPEC   IS C      AT  22
NSPEC   IS RC     AT  23
NSPEC   IS R      AT  24
NSPEC   IS R      AT  25
NSPEC   IS R      AT  26
NSPEC   IS R      AT  27
NSPEC   IS R      AT  28
NSPEC   IS R      AT  29
NSPEC   IS C      AT  30
NSPEC   IS C      AT  31
NSPEC   IS C      AT  32
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  17 18 19 20 21 22 23 30 31 33 34
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  34

STEREO ATTRIBUTES: NONE


=> s l1
SAMPLE SEARCH INITIATED 12:15:55 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      0 TO ITERATE

100.0% PROCESSED       0 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             0 TO        0
PROJECTED ANSWERS:                0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:15:59 FILE 'REGISTRY'
```

```
FULL SCREEN SEARCH COMPLETED -     35 TO ITERATE

100.0% PROCESSED      35 ITERATIONS                              9 ANSWERS
SEARCH TIME: 00.00.01

L3             9 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   157.94     158.15

FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
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FILE COVERS 1907 - 30 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004  (20040329/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l3/prep
            10 L3
       3128003 PREP/RL
L4             8 L3/PREP
                 (L3 (L) PREP/RL)

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     2.36     160.51

FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
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STRUCTURE FILE UPDATES:   29 MAR 2004  HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES:  29 MAR 2004  HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
```

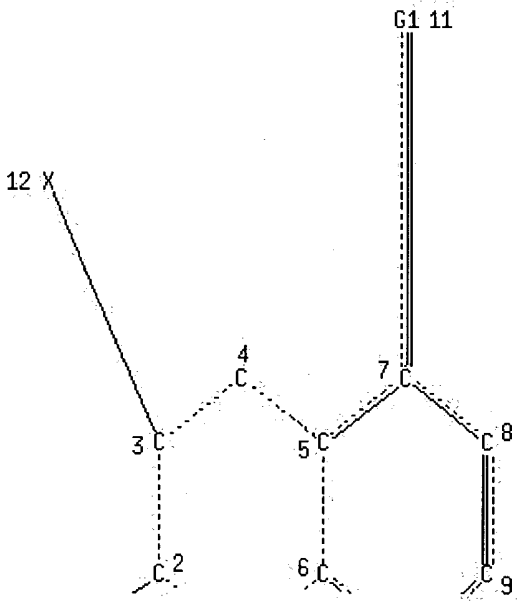
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

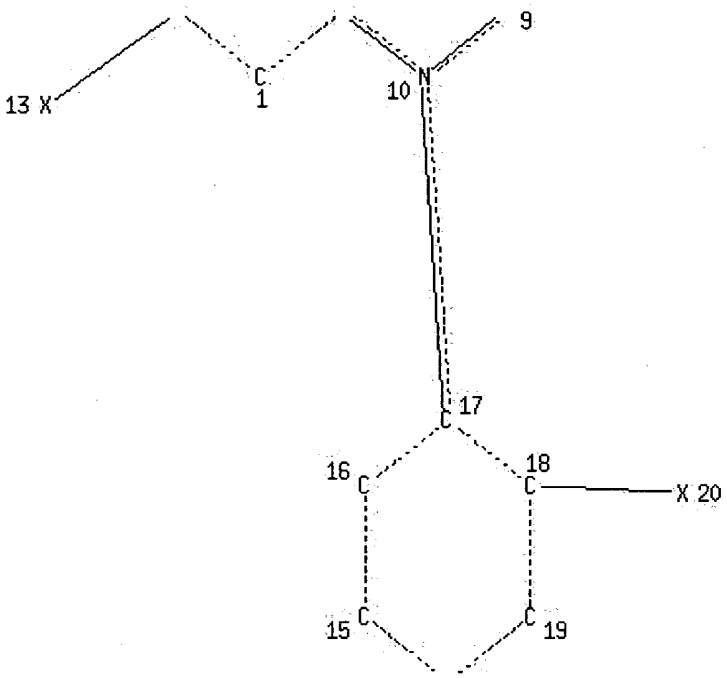
Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
L5 STRUCTURE UPLOADED

=> d l5
L5 HAS NO ANSWERS
L5 STR
0 22 S 23
Page 1-A




Page 1-B




Page 2-B


Page 3-B
VAR G1=22/23
NODE ATTRIBUTES:

| | | | |
|---|---|---|---|
| NSPEC | IS R | AT | 1 |
| NSPEC | IS R | AT | 2 |
| NSPEC | IS R | AT | 3 |
| NSPEC | IS R | AT | 4 |
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MLEVEL IS CLASS AT 12 13 20 21 22 23

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE


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SAMPLE SEARCH INITIATED 12:18:16 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    135 TO ITERATE

100.0% PROCESSED     135 ITERATIONS                          10 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         2003 TO     3397
PROJECTED ANSWERS:              11 TO      389

L6            10 SEA SSS SAM L5

=> s l5 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:18:21 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   2864 TO ITERATE

100.0% PROCESSED    2864 ITERATIONS                         147 ANSWERS
SEARCH TIME: 00.00.01

L7           147 SEA SSS FUL L5

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               156.68     317.19

FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
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strictly prohibited.

FILE COVERS 1907 - 30 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004  (20040329/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
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=> s l7/rct
           110 L7
       2608101 RCT/RL
L8          97 L7/RCT
                (L7 (L) RCT/RL)

=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1               STRUCTURE UPLOADED
L2             0 S L1
L3             9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4             8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5               STRUCTURE UPLOADED
L6            10 S L5
L7           147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8             97 S L7/RCT

=> s l8 and l4
L9             2 L8 AND L4

=> d l9, ibib abs hitstr, 1-2

L9   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:         1993:517227  HCAPLUS
DOCUMENT NUMBER:          119:117227
TITLE:                    Preparation of azabicycloalkylquinolones and
                          -naphthyridinones as antibacterials
INVENTOR(S):              Brighty, Katherine E.
PATENT ASSIGNEE(S):       Pfizer Inc., USA
SOURCE:                   U.S., 42 pp. Cont.-in-part of U.S. Ser. No. 551,212,
                          abandoned.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
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| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5164402 | A | 19921117 | US 1991-650835 | 19910204 |
| US 5229396 | A | 19930720 | US 1992-919477 | 19920724 |
| US 5266569 | A | 19931130 | US 1993-12202 | 19930202 |
| US 5391763 | A | 19950221 | US 1993-88999 | 19930826 |
| PRIORITY APPLN. INFO.: | | | US 1990-551212 | 19900711 |
| | | | US 1991-650835 | 19910204 |
| | | | US 1992-919477 | 19920724 |
| | | | US 1993-12202 | 19930202 |

OTHER SOURCE(S): MARPAT 119:117227
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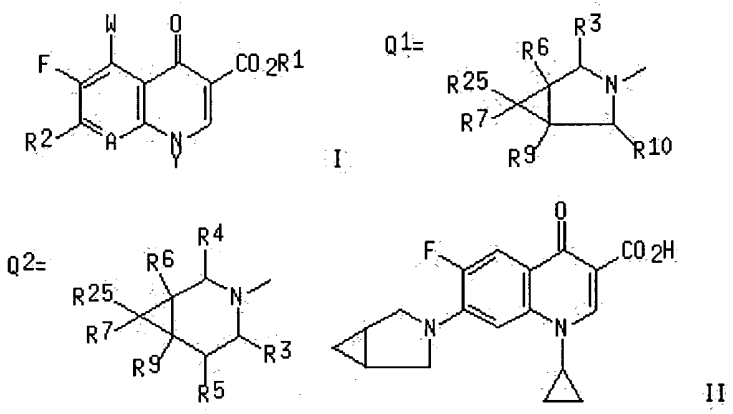
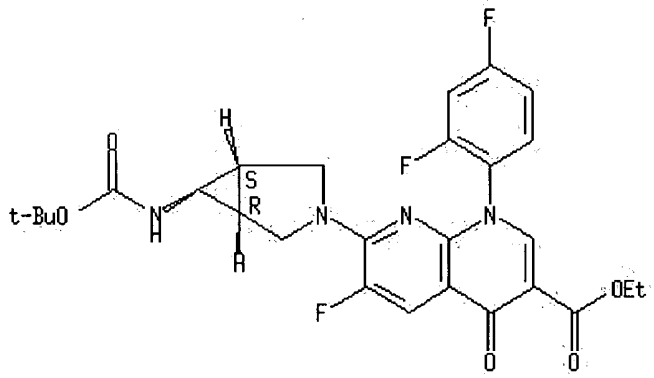



AB Title compds. [I; R1 = H, alkyl, pharmaceutically acceptable cation; Y = Et, Me3C, vinyl cyclopropyl, FCH2CH2, 4-FC6H4, 2,4-F2C6H34; W = F, Cl, Br, alkyl, alkoxy, (methyl)amino; A = CH, CCl, C(OMe), CMe, CCN, N; AY = atoms to form a (0-or double bond-contg.) (substituted) 5-6 membered ring; R2 = Q1, Q2; R3, R4, R5, R6, R7, R9 = H, Me, CH2NH2, CH2NHMe, CH2NHEt; R5, R6, R1, R9 may also = NH2, NHMe, NHEt; ≤3 of R3, R4, R6, R7, R9, R10, R25 ≠ H; if 3 of these ≠ H, ≥1 of them = Me], were prepd. as antibacterials (no data). Thus, 3-azabicyclo[3.1.0]hexane hydrochloride was heated with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinolinecarboxylic acid and Et3N in MgSO to give title compd. II.

IT **134575-66-9P 134575-70-5P 134575-81-8P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. of, as intermediate for antibacterial)

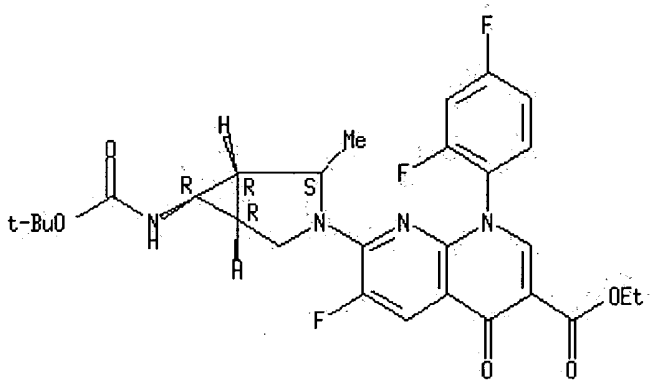
RN 134575-66-9 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]amino]-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



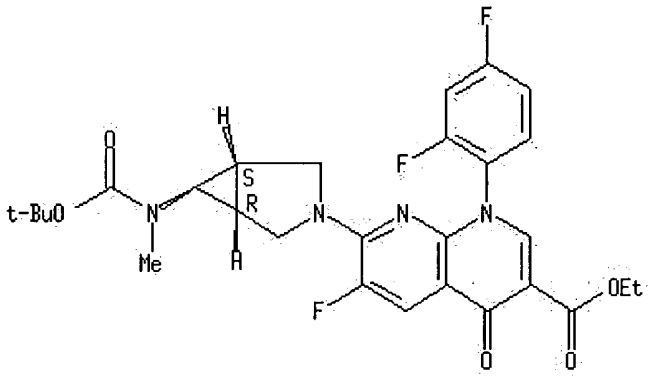

RN 134575-70-5 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methyl-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,2β,5α,6.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

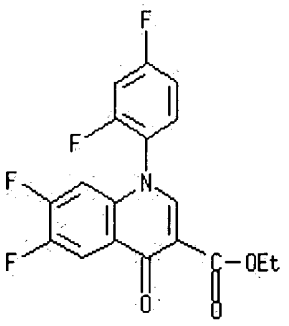


RN 134575-81-8 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]methylamino]-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT 108138-17-6
RL: **RCT (Reactant)**; RACT (Reactant or reagent)
(reaction of, in prepn. of antibacterial)
RN 108138-17-6 HCAPLUS
CN 3-Quinolinecarboxylic acid, 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



L9 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1991:632216 HCAPLUS
DOCUMENT NUMBER: 115:232216

TITLE: Preparation of 7-(azabicycloalkyl)quinolone- and -naphthyridonecarboxylates as antibacterials
INVENTOR(S): Brighty, Katherine Elizabeth
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Eur. Pat. Appl., 73 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 413455 | A2 | 19910220 | EP 1990-308331 | 19900730 |
| EP 413455 | A3 | 19911009 | | |
| EP 413455 | B1 | 19950621 | | |
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| WO 9102526 | A1 | 19910307 | WO 1989-US3489 | 19890816 |
| W: FI, HU, NO, SU, US | | | | |
| HU 59919 | A2 | 19920728 | HU 1992-460 | 19890816 |
| HU 219403 | B | 20010428 | | |
| RU 2049777 | C1 | 19951210 | RU 1989-5011662 | 19890816 |
| ES 2074131 | T3 | 19950901 | ES 1990-308331 | 19900730 |
| IL 95331 | A1 | 19950731 | IL 1990-95331 | 19900809 |
| CA 2023217 | AA | 19910217 | CA 1990-2023217 | 19900814 |
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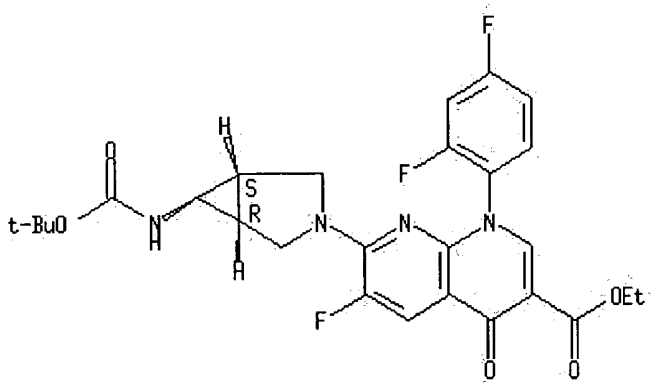
| PL 166381 | B1 | 19950531 | PL 1990-286484 | 19900814 |
| AU 9061042 | A1 | 19910221 | AU 1990-61042 | 19900815 |
| AU 623801 | B2 | 19920521 | | |
| CN 1049501 | A | 19910227 | CN 1990-106794 | 19900815 |
| CN 1025192 | B | 19940629 | | |
| DD 298399 | A5 | 19920220 | DD 1990-343474 | 19900815 |
| ZA 9006450 | A | 19920325 | ZA 1990-6450 | 19900815 |
| JP 03086875 | A2 | 19910411 | JP 1990-216461 | 19900816 |
| JP 07002734 | B4 | 19950118 | | |
| CZ 281127 | B6 | 19960612 | CZ 1990-4027 | 19900816 |
| NO 9200599 | A | 19920414 | NO 1992-599 | 19920214 |
| JP 07149758 | A2 | 19950613 | JP 1994-157008 | 19940708 |
| JP 08019099 | B4 | 19960228 | | |
| FI 9604520 | A | 19961111 | FI 1996-4520 | 19961111 |

PRIORITY APPLN. INFO.: WO 1989-US3489 A 19890816
FI 1992-632 A 19920214

OTHER SOURCE(S): MARPAT 115:232216
GI For diagram(s), see printed CA Issue.
AB Title compds. [I; R1 = H, alkyl, cation; Y = Et, Me3C, H2C:CH cyclopropyl, FCH2CH2, 4-FC6H4, 2,4-F2C6H3; W = H, F, Cl, Br, alkyl, alkoxy, amino, aminomethyl; A = CH, CF, CCl, COMe, CMe, CCN, N; AY = atoms to form a 5- or 6-membered ring, optionally contg. O or a double bond and optionally substituted by Me or :CH2; R2 = (Me-, H2NCH2-, MeNHCH2-, EtNHCH2-, etc. substituted) Q1, Q2], were prepd. as antibacterials (no data). Thus, a mixt. of 3-azabicyclo[3.1.0]hexane hydrochloride, 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, Et3N, and Me2SO was heated 18 h to give title compd. II.
IT **134575-66-9P 134575-70-5P 134575-81-8P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. of, as intermediate for (azabicycloalkyl)quinolone)
RN 134575-66-9 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]amino]-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,5α,6α)- (9CI) (CA

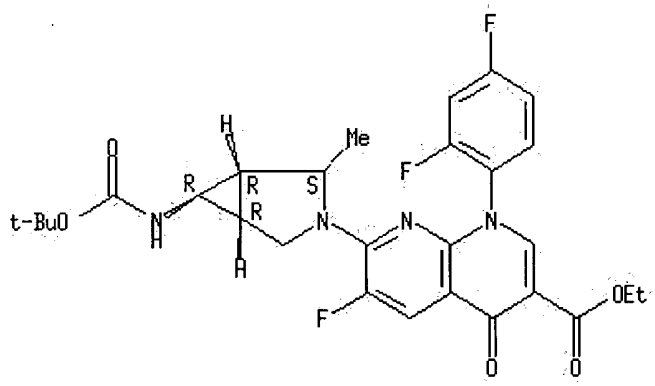
INDEX NAME)

Relative stereochemistry.



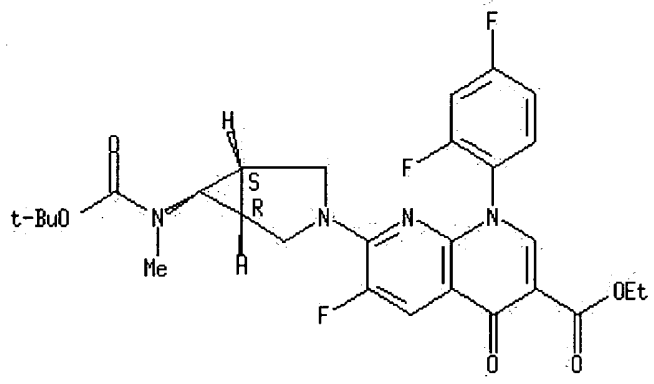
RN 134575-70-5 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methyl-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,2β,5α,6.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 134575-81-8 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]methylamino]-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,5α,6α)- (9CI) (CA INDEX NAME)

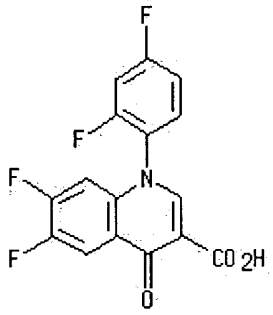
Relative stereochemistry.



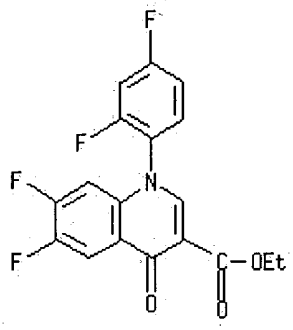
IT 103995-01-3 108138-17-6

RL: **RCT (Reactant)**; RACT (Reactant or reagent)
(reaction of, in prepn. of (azabicycloalkyl)quinolone antibacterial)

RN 103995-01-3 HCAPLUS
CN 3-Quinolinecarboxylic acid, 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo- (9CI) (CA INDEX NAME)



RN 108138-17-6 HCAPLUS
CN 3-Quinolinecarboxylic acid, 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



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|---|---|---|
| FULL ESTIMATED COST | 14.23 | 331.42 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -1.39 | -1.39 |

FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

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  This file supports REG1stRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1             STRUCTURE UPLOADED
L2           0 S L1
L3           9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4           8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5             STRUCTURE UPLOADED
L6          10 S L5
L7         147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8          97 S L7/RCT
L9           2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004

=> s l3 and l7
             0 L3
             0 L7
L10          0 L3 AND L7

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.42     331.84

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                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -1.39

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provided by InfoChem.

STRUCTURE FILE UPDATES:   29 MAR 2004  HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES:  29 MAR 2004  HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
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information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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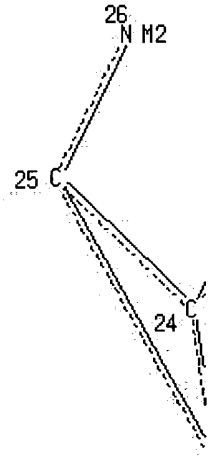
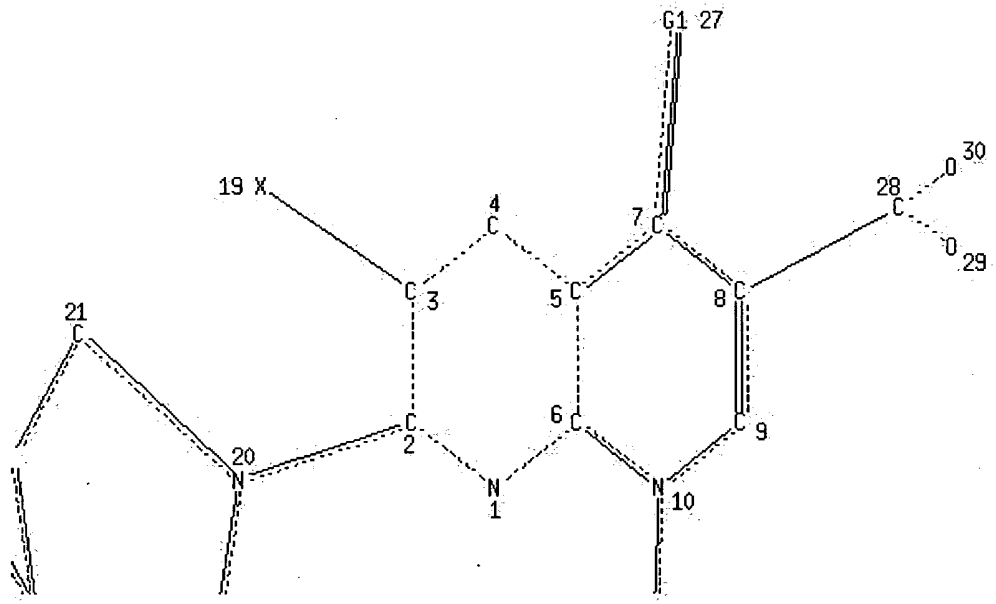



Page 1-A

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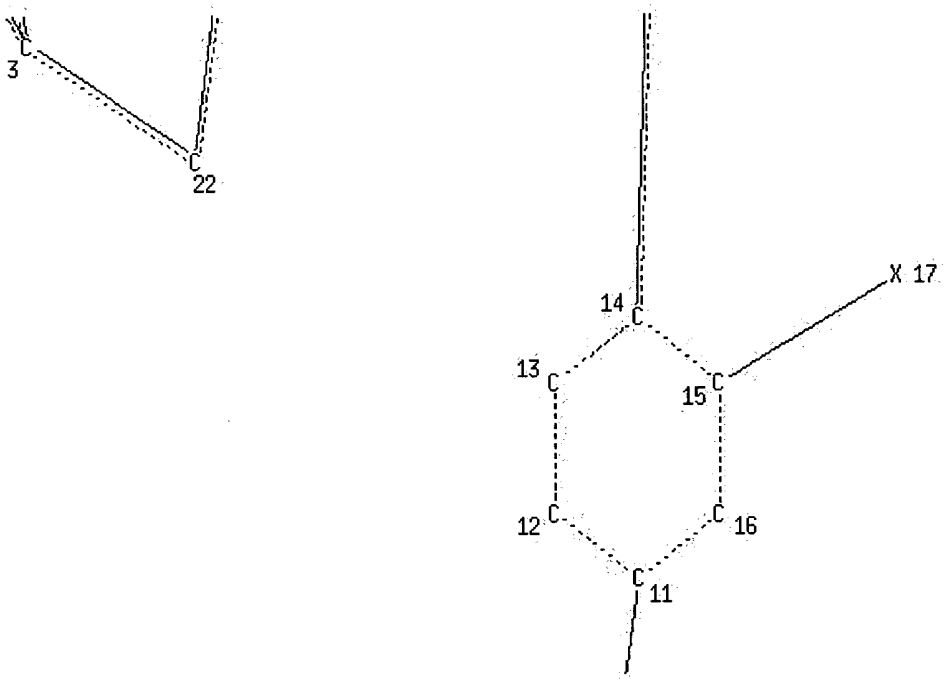
Page 2-A




Page 2-B


Page 3-B
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NSPEC   IS C      AT  29
NSPEC   IS C      AT  30
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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS  32

STEREO ATTRIBUTES: NONE


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SAMPLE SCREEN SEARCH COMPLETED -      6 TO ITERATE

100.0% PROCESSED       6 ITERATIONS                              1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            6 TO      266
PROJECTED ANSWERS:               1 TO       80

L12           1 SEA SSS SAM L11

=> s l11 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:23:40 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    114 TO ITERATE

100.0% PROCESSED     114 ITERATIONS                             21 ANSWERS
SEARCH TIME: 00.00.01

L13          21 SEA SSS FUL L11

=> file hcaplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                157.52     489.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                 0.00      -1.39

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```

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FILE COVERS 1907 - 30 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004 (20040329/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> **s l13**
L14 793 L13

=> **s l13/prep**
793 L13
3128003 PREP/RL
L15 27 L13/PREP
(L13 (L) PREP/RL)

=> **file reg**

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 2.36 | 491.72 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | 0.00 | -1.39 |

FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 29 MAR 2004 HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES: 29 MAR 2004 HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

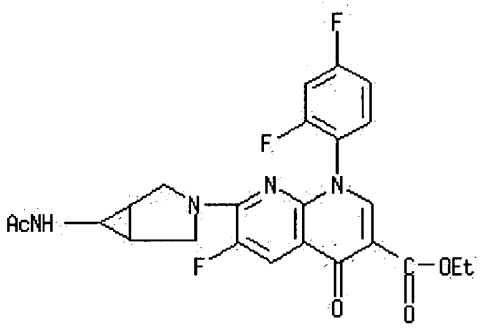
=> **e methanesulfonic acid**
E1 1 METHANESULFONATOTHIAZOLE/BI
E2 43390 METHANESULFONIC/BI
E3 0 --> METHANESULFONIC ACID/BI
E4 38 METHANESULFONIMID/BI
E5 3 METHANESULFONIMIDAMID/BI
E6 3 METHANESULFONIMIDAMIDATO/BI
E7 33 METHANESULFONIMIDAMIDE/BI

```
E8            4      METHANESULFONIMIDATE/BI
E9            1      METHANESULFONIMIDATO/BI
E10           3      METHANESULFONIMIDE/BI
E11          37      METHANESULFONIMIDIC/BI
E12          35      METHANESULFONIMIDO/BI

=> e methanesulfonic acid/cn
E1            1      METHANESULFONATE SULFONATASE MSUD (PSEUDOMONAS AERUGINOSA ST
                     RAIN PAO1 GENE MSUD)/CN
E2            1      METHANESULFONATE SULFONATASE; MSUD (MESORHIZOBIUM LOTI STRAI
                     N MAFF303099 GENE MLR5216)/CN
E3            1 --> METHANESULFONIC ACID/CN
E4            1      METHANESULFONIC ACID ((5R)-3-(3-FLUORO-4-(TETRAHYDROTHIOPYRA
                     N-4-YL)PHENYL)-2-OXOOXAZOLIDIN-5-YL)METHYL ESTER/CN
E5            1      METHANESULFONIC ACID ((5R)-3-(4-((1,4-DIBENZYLPIPERAZIN-2-YL
                     METHYL)ETHYLAMINO)-3-FLUOROPHENYL)-2-OXOOXAZOLIDIN-5-YL)METH
                     YL ESTER/CN
E6            1      METHANESULFONIC ACID ((5R)-3-(4-(3,6-DIHYDRO-2H-THIOPYRAN-4-
                     YL)-3,5-DIFLUOROPHENYL)-2-OXOOXAZOLIDIN-5-YL)METHYL ESTER/CN
E7            1      METHANESULFONIC ACID ((5R)-3-(4-(3,6-DIHYDRO-2H-THIOPYRAN-4-
                     YL)-3-FLUOROPHENYL)-2-OXOOXAZOLIDIN-5-YL)METHYL ESTER/CN
E8            1      METHANESULFONIC ACID (1R,2R)-2-(4-(6-TRIFLUOROMETHYLBENZO(B)
                     THIOPHEN-3-YL)PIPERAZIN-1-YLMETHYL)CYCLOPROPYLMETHYL ESTER/C
                     N
E9            1      METHANESULFONIC ACID (2-(2-AZIDOETHYLTHIO)ETHYL) ESTER/CN
E10           1      METHANESULFONIC ACID (2-(PYRIDIN-2-YL)-3-(QUINOLIN-4-YL)-5,6
                     -DIHYDRO-4H-PYRROLO(1,2-B)PYRAZOL-6-YL)METHYL ESTER/CN
E11           1      METHANESULFONIC ACID (2S)-TERT-BUTOXYCARBONYLAMINO-(1S)-(2-(
                     1,3)DIOXAN-2-YLETHYL)-3-(3-FLUOROPHENYL)PROPYL ESTER/CN
E12           1      METHANESULFONIC ACID (3-(4-BROMO-3-FLUOROPHENYL)-4,5-DIHYDRO
                     ISOXAZOL-5-YL)METHYL ESTER/CN

=> d l3

L3   ANSWER 1 OF 9  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   323575-31-1  REGISTRY
CN   1,8-Naphthyridine-3-carboxylic acid, 7-[6-(acetylamino)-3-
     azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-
     oxo-, ethyl ester (9CI)  (CA INDEX NAME)
FS   3D CONCORD
MF   C24 H21 F3 N4 O4
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT, USPATFULL
```




```
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

              1 REFERENCES IN FILE CA (1907 TO DATE)
```

```
                1 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1              STRUCTURE UPLOADED
L2            0 S L1
L3            9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4            8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5              STRUCTURE UPLOADED
L6           10 S L5
L7          147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8           97 S L7/RCT
L9            2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10           0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11             STRUCTURE UPLOADED
L12           1 S L11
L13          21 S L11 FULL

     FILE 'HCAPLUS' ENTERED AT 12:23:44 ON 30 MAR 2004
L14         793 S L13
L15          27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
               E METHANESULFONIC ACID
               E METHANESULFONIC ACID/CN

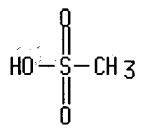
=> e methanesulfonic acid/cn
E1            1     METHANESULFONATE SULFONATASE MSUD (PSEUDOMONAS AERUGINOSA ST
                    RAIN PAO1 GENE MSUD)/CN
E2            1     METHANESULFONATE SULFONATASE; MSUD (MESORHIZOBIUM LOTI STRAI
                    N MAFF303099 GENE MLR5216)/CN
E3            1 --> METHANESULFONIC ACID/CN
E4            1     METHANESULFONIC ACID ((5R)-3-(3-FLUORO-4-(TETRAHYDROTHIOPYRA
                    N-4-YL)PHENYL)-2-OXOOXAZOLIDIN-5-YL)METHYL ESTER/CN
E5            1     METHANESULFONIC ACID ((5R)-3-(4-((1,4-DIBENZYLPIPERAZIN-2-YL
                    METHYL)ETHYLAMINO)-3-FLUOROPHENYL)-2-OXOOXAZOLIDIN-5-YL)METH
                    YL ESTER/CN
E6            1     METHANESULFONIC ACID ((5R)-3-(4-(3,6-DIHYDRO-2H-THIOPYRAN-4-
                    YL)-3,5-DIFLUOROPHENYL)-2-OXOOXAZOLIDIN-5-YL)METHYL ESTER/CN
E7            1     METHANESULFONIC ACID ((5R)-3-(4-(3,6-DIHYDRO-2H-THIOPYRAN-4-
                    YL)-3-FLUOROPHENYL)-2-OXOOXAZOLIDIN-5-YL)METHYL ESTER/CN
E8            1     METHANESULFONIC ACID (1R,2R)-2-(4-(6-TRIFLUOROMETHYLBENZO(B)
                    THIOPHEN-3-YL)PIPERAZIN-1-YLMETHYL)CYCLOPROPYLMETHYL ESTER/C
                    N
E9            1     METHANESULFONIC ACID (2-(2-AZIDOETHYLTHIO)ETHYL) ESTER/CN
E10           1     METHANESULFONIC ACID (2-(PYRIDIN-2-YL)-3-(QUINOLIN-4-YL)-5,6
```

```
                    -DIHYDRO-4H-PYRROLO(1,2-B)PYRAZOL-6-YL)METHYL ESTER/CN
E11           1     METHANESULFONIC ACID (2S)-TERT-BUTOXYCARBONYLAMINO-(1S)-(2-(
                    1,3)DIOXAN-2-YLETHYL)-3-(3-FLUOROPHENYL)PROPYL ESTER/CN
E12           1     METHANESULFONIC ACID (3-(4-BROMO-3-FLUOROPHENYL)-4,5-DIHYDRO
                    ISOXAZOL-5-YL)METHYL ESTER/CN

=> s e3
L16           1 "METHANESULFONIC ACID"/CN

=> d l16

L16  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   75-75-2  REGISTRY
CN   Methanesulfonic acid (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   MCAT 1201
CN   Methylsulfonic acid
CN   NSC 3718
FS   3D CONCORD
DR   125756-91-4, 98527-29-8, 115449-98-4, 62203-24-1, 87128-90-3, 44209-64-5,
     44209-72-5
MF   C H4 O3 S
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,
       CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DETHERM*, DIPPR*, EMBASE,
       ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*,
       IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC,
       PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT,
       USPAT2, USPATFULL, VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)
```



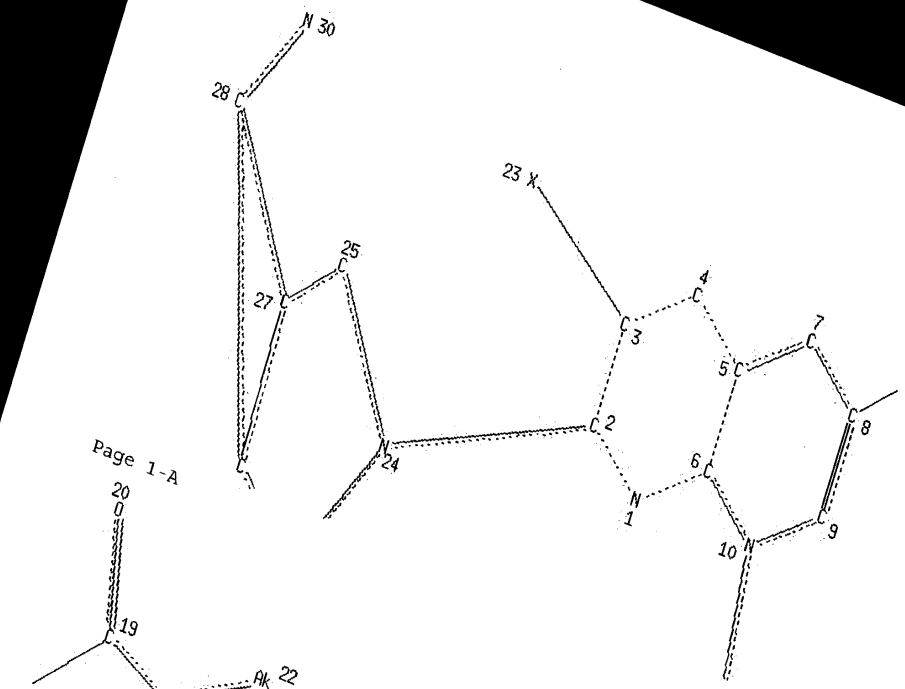
```
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

            4363 REFERENCES IN FILE CA (1907 TO DATE)
             135 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            4372 REFERENCES IN FILE CAPLUS (1907 TO DATE)
              21 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=>
L17      STRUCTURE UPLOADED

=>
L18      STRUCTURE UPLOADED

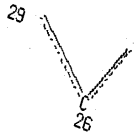
=> d l18
L18 HAS NO ANSWERS
L18              STR
```

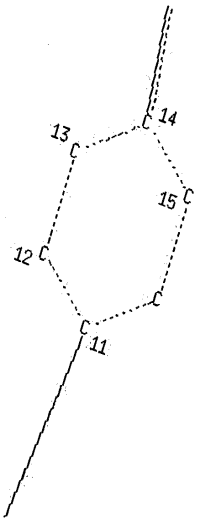



Page 1-A




Page 1-B




Page 2-A


Page 2-B


Page 3-A

```
NODE ATTRIBUTES:
NSPEC   IS R      AT   1
NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
NSPEC   IS R      AT   4
NSPEC   IS R      AT   5
NSPEC   IS R      AT   6
NSPEC   IS R      AT   7
NSPEC   IS R      AT   8
NSPEC   IS R      AT   9
NSPEC   IS R      AT  10
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
NSPEC   IS R      AT  14
NSPEC   IS R      AT  15
NSPEC   IS R      AT  16
NSPEC   IS C      AT  17
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
NSPEC   IS C      AT  21
NSPEC   IS C      AT  22
NSPEC   IS C      AT  23
NSPEC   IS R      AT  24
NSPEC   IS R      AT  25
NSPEC   IS R      AT  26
NSPEC   IS R      AT  27
NSPEC   IS R      AT  28
NSPEC   IS R      AT  29
NSPEC   IS C      AT  30
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  17 18 19 20 21 22 23 30
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE


=> s l18/rct
QUALIFICATION NOT VALID FOR L18
Field code qualifications can only be applied to text
```

terms.

=> **file hcaplus**

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 14.69 | 506.41 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | 0.00 | -1.39 |

FILE 'HCAPLUS' ENTERED AT 12:33:37 ON 30 MAR 2004
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE COVERS 1907 - 30 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004 (20040329/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> **s l18/rct**
SEARCH PROFILE NOT SUPPORTED FOR AUTOMATED SEARCH AND CROSSOVER
The search profile contains L-numbers or saved item names that include chemical substance terms, chemical structures, or structure screen sets. If you are in a single file environment using the CA file (CA, HCA, ZCA, CAPLUS, HCAPLUS, ZCAPLUS), enter HELP FIRST at an arrow prompt (=>) for information about the REG1stRY automated search and crossover feature. REG1stRY supports the following search profiles:

Example 1:
```
   => ACT SCRSTR/Q
   L3              STR
   L4              SCR 2127
   L5              QUE  L3 NOT L4

   These searches are supported:
   S  L5/REG
   S  SCRSTR/Q/REG
   S  (L3 NOT L4)/REG

   These searches are not supported:
   S  L5
   S  SCRSTR/Q
```

Example 2:
```
   => ACT SCRSTR2/Q
```

```
   L6              STR
   L7              SCR 2127
   L8              QUE  L6
   L9              QUE  L7
   L10             QUE  L8 NOT L9

   This search is supported:
   S  (L6 NOT L7)/REG

   These searches are not supported:
   S  L10
   S  L10/REG
   S  SCRSTR2/Q
   S  SCRSTR2/Q/REG
   S  L8 NOT L9
   S  (L8 NOT L9)/REG

=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1              STRUCTURE UPLOADED
L2            0 S L1
L3            9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4            8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5              STRUCTURE UPLOADED
L6           10 S L5
L7          147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8           97 S L7/RCT
L9            2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10           0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11             STRUCTURE UPLOADED
L12           1 S L11
L13          21 S L11 FULL

     FILE 'HCAPLUS' ENTERED AT 12:23:44 ON 30 MAR 2004
L14         793 S L13
L15          27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
                E METHANESULFONIC ACID
                E METHANESULFONIC ACID/CN
                E METHANESULFONIC ACID/CN
L16           1 S E3
L17             STRUCTURE UPLOADED
L18             STRUCTURE UPLOADED

     FILE 'HCAPLUS' ENTERED AT 12:33:37 ON 30 MAR 2004
```

```
=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         2.36     508.77

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -1.39

FILE 'REGISTRY' ENTERED AT 12:33:54 ON 30 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   29 MAR 2004  HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES:  29 MAR 2004  HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> s l17
SAMPLE SEARCH INITIATED 12:33:58 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -  15057 TO ITERATE

  6.6% PROCESSED    1000 ITERATIONS                          44 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       293795 TO   308485
PROJECTED ANSWERS:           11706 TO    14794

L19          44 SEA SSS SAM L17

=> s l18 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:34:04 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    163 TO ITERATE

100.0% PROCESSED     163 ITERATIONS                          17 ANSWERS
SEARCH TIME: 00.00.01

L20          17 SEA SSS FUL L18

=> s l19 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
```

```
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:34:13 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 301821 TO ITERATE

100.0% PROCESSED  301821 ITERATIONS                          15041 ANSWERS
SEARCH TIME: 00.00.04

L21        15041 SEA SSS FUL L17

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   310.42     819.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -1.39

FILE 'HCAPLUS' ENTERED AT 12:34:20 ON 30 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 30 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004  (20040329/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l21/rct
         19281 L21
       2608101 RCT/RL
L22       2087 L21/RCT
                (L21 (L) RCT/RL)

=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1              STRUCTURE UPLOADED
L2            0 S L1
L3            9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4            8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
```

```
L5              STRUCTURE UPLOADED
L6           10 S L5
L7          147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8           97 S L7/RCT
L9            2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10           0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11             STRUCTURE UPLOADED
L12           1 S L11
L13          21 S L11 FULL

     FILE 'HCAPLUS' ENTERED AT 12:23:44 ON 30 MAR 2004
L14         793 S L13
L15          27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
                E METHANESULFONIC ACID
                E METHANESULFONIC ACID/CN
                E METHANESULFONIC ACID/CN
L16           1 S E3
L17             STRUCTURE UPLOADED
L18             STRUCTURE UPLOADED

     FILE 'HCAPLUS' ENTERED AT 12:33:37 ON 30 MAR 2004

     FILE 'REGISTRY' ENTERED AT 12:33:54 ON 30 MAR 2004
L19          44 S L17
L20          17 S L18 FULL
L21       15041 S L19 FULL

     FILE 'HCAPLUS' ENTERED AT 12:34:20 ON 30 MAR 2004
L22        2087 S L21/RCT

=> s l22 and l15
L23           5 L22 AND L15

=> d l23, ibib abs hitstr, 1-5

L23  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:         2001:91540  HCAPLUS
DOCUMENT NUMBER:          134:147591
TITLE:                    Preparation of trovafloxacin
INVENTOR(S):              Chiu, Charles K.; Wint, Lewin T.
PATENT ASSIGNEE(S):       Pfizer Inc., USA
SOURCE:                   U.S., 7 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
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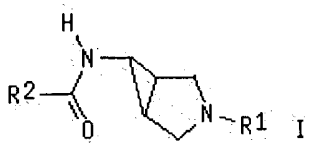
| | | | | | |
|---|---|---|---|---|---|
| US 6184380 | B1 | 20010206 | US 1999-236737 | | 19990125 |
| US 2002095043 | A1 | 20020718 | US 2002-87756 | | 20020304 |
| PRIORITY APPLN. INFO.: | | | US 1998-71601P | P | 19980116 |
| | | | US 1999-236737 | A3 | 19990125 |
| | | | US 2000-718324 | A3 | 20001122 |

OTHER SOURCE(S): CASREACT 134:147591; MARPAT 134:147591
GI



I

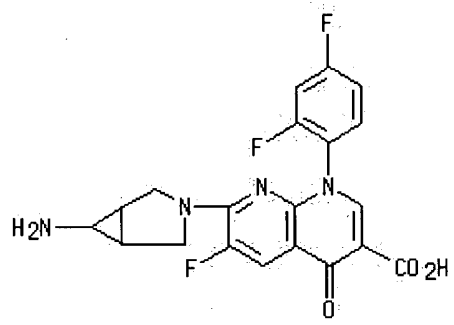
AB The title process comprises use of azabicyclohexanes I [R1 = (un)substituted CH2Ph; R2 = CF3, alkyl, (un)substituted Ph] and a 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid alkyl ester.

IT **323575-32-2P**
RL: IMF (Industrial manufacture); **RCT (Reactant)**; SPN (Synthetic preparation); **PREP (Preparation)**; RACT (Reactant or reagent)
(prepn. of trovafloxacin)

RN 323575-32-2 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

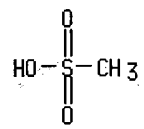
CRN 308353-09-5
CMF C20 H15 F3 N4 O3



Double Patenting

CM 2

CRN 75-75-2
CMF C H4 O3 S



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:307680 HCAPLUS
DOCUMENT NUMBER: 133:222629
TITLE: Synthesis of trovafloxacin using various (1α,5α,6α)-3-azabicyclo[3.1.0]hexane derivatives
AUTHOR(S): Norris, Timothy; Braish, Tamim F.; Butters, Michael; DeVries, Keith M.; Hawkins, Joel M.; Massett, Stephen S.; Rose, Peter R.; Santafianos, Dinos; Sklavounos, Constantine
CORPORATE SOURCE: Pfizer Central Research Laboratories, Groton, CT, 06340, USA
SOURCE: Perkin 1 (2000), (10), 1615-1622
CODEN: PERKF9
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:222629
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Trovafloxacin, a novel broad spectrum antibacterial, contains the unusual (1α,5α,6α)-3-azabicyclo[3.1.0]hexane ring system. The prototype of the industrial synthesis of this ring system and possible mechanistic pathways to exclusive formation of the exo or 6α-nitro deriv. I are described, which leads to the key 6α-nitro-3-azabicyclo[3.1.0]hexane intermediate [II; R1 = NO2, R2 = Bn (III)]. The synthesis of II (R1 = NH2, R2 = H) and useful protected exo 6-amino derivs. II (R1 = BOCNH, PHCH:N; R2 = H) follows from III. These can be coupled with the 7-chloronaphthyridone to yield protected trovafloxacin compds. IV [R3 = BOCNH, NH2, PHCH:N] in good yield. Removal of protecting groups from IV with methanesulfonic acid yields trovafloxacin mesylate from which the trovafloxacin zwitterion can be liberated with base treatment. The zwitterion can also be prepd. directly from the tosylate salt of II (R1 = NH2, R2 = H) and naphthyridone-2-carboxylic acid V.

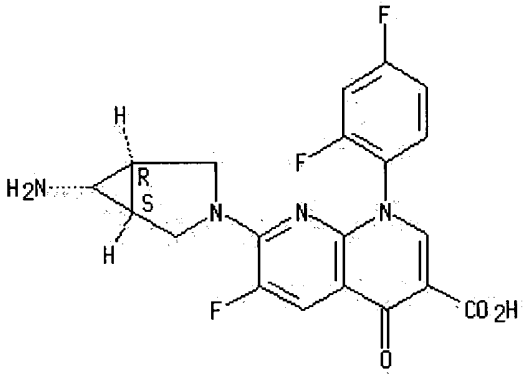
IT **147059-75-4P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); **PREP (Preparation)**; RACT (Reactant or reagent)
(stereoselective prepn of antibacterial agent trovafloxacin)

RN 147059-75-4 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, (1α,5α,6α)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

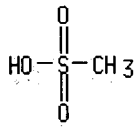
CRN 147059-72-1
CMF C20 H15 F3 N4 O3

Relative stereochemistry.



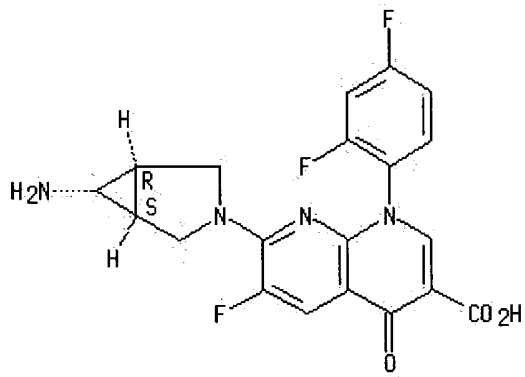
CM 2

CRN 75-75-2
CMF C H4 O3 S



IT **147059-72-1P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(stereoselective prepn of antibacterial agent trovafloxacin)
RN 147059-72-1 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

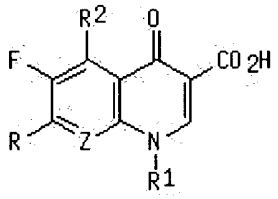
Full Text | Citing References

ACCESSION NUMBER: 2000:84387 HCAPLUS
DOCUMENT NUMBER: 132:122609
TITLE: Preparation of trovafloxacin and analogs
INVENTOR(S): Norris, Timothy
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 976749 | A1 | 20000202 | EP 1999-305577 | 19990714 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| US 6114531 | A | 20000905 | US 1999-324385 | 19990602 |
| JP 2000053646 | A2 | 20000222 | JP 1999-210179 | 19990726 |
| CA 2278845 | C | 20030708 | CA 1999-2278845 | 19990726 |
| AU 9941169 | A1 | 20000217 | AU 1999-41169 | 19990727 |
| KR 2000012002 | A | 20000225 | KR 1999-30560 | 19990727 |
| BR 9903003 | A | 20000321 | BR 1999-3003 | 19990727 |
| CN 1247865 | A | 20000322 | CN 1999-119527 | 19990727 |
| ZA 9904814 | A | 20010129 | ZA 1999-4814 | 19990727 |
| RU 2167867 | C2 | 20010527 | RU 1999-116268 | 19990727 |
| MX 9907034 | A | 20000228 | MX 1999-7034 | 19990728 |

PRIORITY APPLN. INFO.: US 1998-94440P P 19980728
OTHER SOURCE(S): CASREACT 132:122609; MARPAT 132:122609
GI




I

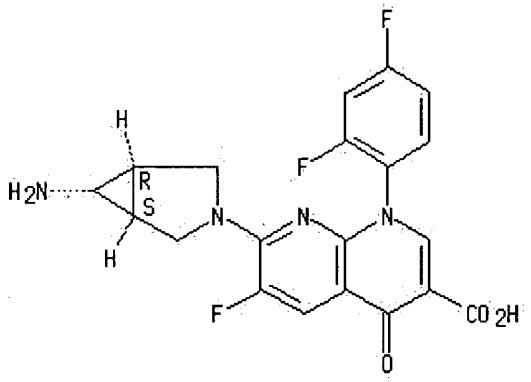
AB Title compds. [I; R = H2N(CH2)nZ1; R1 = Et, CMe3, cyclopropyl, etc.; R2 = H, F, alkyl, alkoxy, etc.; Z = CH, CF, CR3, N, etc.; R1R3 = atoms to complete a ring; Z1 = 1-aza(bi)cycloalkylene; n = 0 or 1] were prepd. by condensation of I (R = halo) with an acid salt of H2N(CH2)nZ1H.

IT **147059-72-1P**, Trovafloxacin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. of trovafloxacin and analogs)

RN 147059-72-1 HCAPLUS

CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

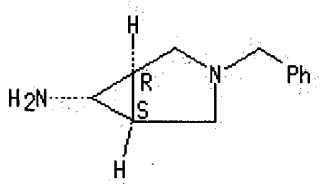


IT 256369-38-7
RL: **RCT (Reactant)**; RACT (Reactant or reagent)
(prepn. of trovafloxacin and analogs)
RN 256369-38-7 HCAPLUS
CN 3-Azabicyclo[3.1.0]hexan-6-amine, 3-(phenylmethyl)-, (1α,5α,6α)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

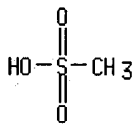
CRN 151860-17-2
CMF C12 H16 N2

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

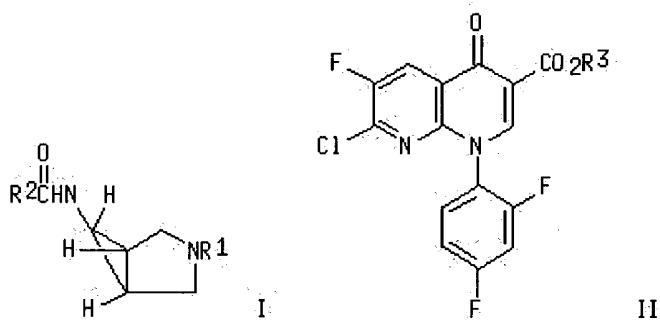
Full Text | Citing References

ACCESSION NUMBER: 1999:460272 HCAPLUS
DOCUMENT NUMBER: 131:116223
TITLE: Process for preparing naphthyridones and intermediates
INVENTOR(S): Chiu, Charles Kwok-Fung; Wint, Lewin Theophilus
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 930297 | A1 | 19990721 | EP 1999-300183 | 19990112 |
| EP 930297 | B1 | 20030423 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AU 9897115 | A1 | 19990805 | AU 1998-97115 | 19981215 |
| JP 11255745 | A2 | 19990921 | JP 1999-5494 | 19990112 |
| SG 76584 | A1 | 20001121 | SG 1999-46 | 19990112 |
| EG 21514 | A | 20011128 | EG 1999-34 | 19990112 |
| TW 483890 | B | 20020421 | TW 1999-88100415 | 19990112 |
| AT 238281 | E | 20030515 | AT 1999-300183 | 19990112 |
| ES 2195513 | T3 | 20031201 | ES 1999-300183 | 19990112 |
| BR 9900066 | A | 20000509 | BR 1999-66 | 19990114 |
| CA 2258960 | C | 20020903 | CA 1999-2258960 | 19990114 |
| CA 2258960 | AA | 19990716 | | |
| NO 9900185 | A | 19990719 | NO 1999-185 | 19990115 |
| CN 1228422 | A | 19990915 | CN 1999-101086 | 19990115 |
| NZ 333769 | A | 20000327 | NZ 1999-333769 | 19990115 |
| ZA 9900277 | A | 20000717 | ZA 1999-277 | 19990115 |
| BG 64094 | B1 | 20031231 | BG 1999-103087 | 19990115 |

PRIORITY APPLN. INFO.: US 1998-71601P P 19980116
OTHER SOURCE(S): CASREACT 131:116223; MARPAT 131:116223
GI

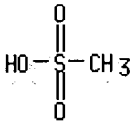



I II

AB 6-Acetamido-3-benzylazabicyclo[3.1.0]hexanes [I; R1 = (un)substituted PhCH2; R2 = C1-6 alkyl, CF3, (un)substituted Ph] are prepd. by redn. of the parent nitro derivs. with Fe powder in AcOH/Me2CHOH and N-acylation of the resulting amines. Debenzylation of I with H in AcOH in the presence of Pd catalyst, condensation of debenzylated intermediates with naphthyridine-3-carboxylate esters (II; R3 = C1-6 alkyl) and hydrolysis of the resulting intermediates (prepn. procedure claimed) with MeSO3H in aq. org. solvents gives trovafloxacin (III), an antibacterial active esp. against gram-pos. bacterial strains, as monomethanesulfonate salt. Thus, III·HO3SMe was prepd. from I (R1 = PhCH2, R2 = Me) and II (R3 = Et) as described above.

IT 75-75-2, Methanesulfonic acid
RL: **RCT (Reactant)**; RACT (Reactant or reagent)
(hydrolysis of naphthyridonecarboxylate deriv.; process for prepg. naphthyridones and trovafloxacin intermediates)

RN 75-75-2 HCAPLUS
CN Methanesulfonic acid (8CI, 9CI) (CA INDEX NAME)

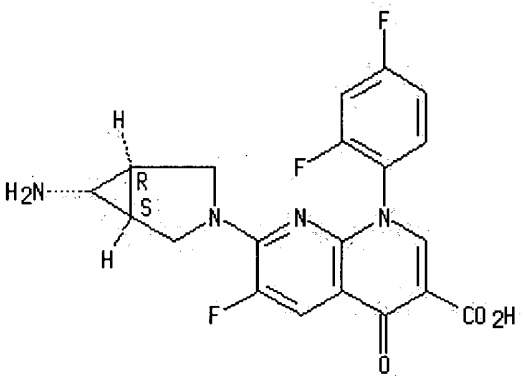


IT **147059-75-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(process for prepg. naphthyridones and trovafloxacin intermediates)
RN 147059-75-4 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, (1α,5α,6α)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

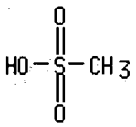
CRN 147059-72-1
CMF C20 H15 F3 N4 O3

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1997:283734 HCAPLUS
DOCUMENT NUMBER: 126:264093
TITLE: Preparation of crystalline forms of trovafloxacin zwitterion
INVENTOR(S): Allen, Douglas John Meldrum; Joseph, David Bruning; Norris, Timothy

PATENT ASSIGNEE(S): Pfizer Inc., USA; Allen, Douglas John Meldrum; Joseph, David Bruning; Norris, Timothy
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9707800 | A1 | 19970306 | WO 1996-IB756 | 19960729 |
| W: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9663676 | A1 | 19970319 | AU 1996-63676 | 19960729 |
| AU 704115 | B2 | 19990415 | | |
| EP 850060 | A1 | 19980701 | EP 1996-923020 | 19960729 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI | | | | |
| CN 1190889 | A | 19980819 | CN 1996-195624 | 19960729 |
| JP 10511692 | T2 | 19981110 | JP 1996-503436 | 19960729 |
| BR 9609998 | A | 19990706 | BR 1996-9998 | 19960729 |
| RU 2144921 | C1 | 20000127 | RU 1998-103873 | 19960729 |
| IL 122651 | A1 | 20000217 | IL 1996-122651 | 19960729 |
| JP 3188476 | B2 | 20010716 | JP 1997-503436 | 19960729 |
| CA 2229786 | C | 20020219 | CA 1996-2229786 | 19960729 |
| TW 386083 | B | 20000401 | TW 1996-85109282 | 19960730 |
| ZA 9607282 | A | 19980302 | ZA 1996-7282 | 19960828 |
| HR 960395 | B1 | 20011231 | HR 1996-960395 | 19960829 |
| US 6066647 | A | 20000523 | US 1998-11725 | 19980129 |
| NO 9800862 | A | 19980227 | NO 1998-862 | 19980227 |

PRIORITY APPLN. INFO.: US 1995-2975P P 19950829
WO 1996-IB756 W 19960729

OTHER SOURCE(S): MARPAT 126:264093

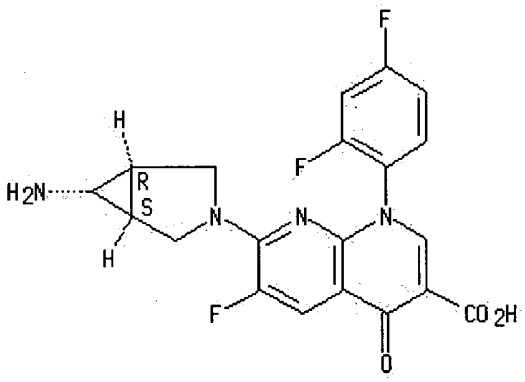
AB Title compds. characterized by x-ray spectra were prepd.

IT **147059-72-1P 188762-12-1P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. of cryst. forms of trovafloxacin zwitterion)

RN 147059-72-1 HCAPLUS

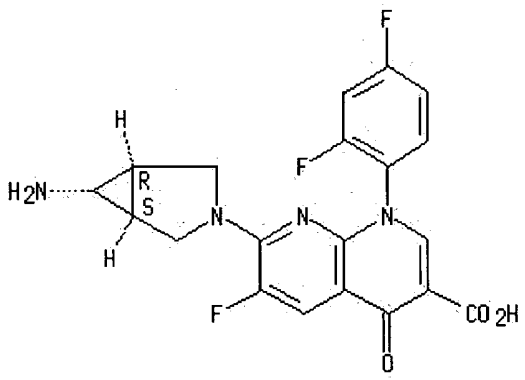
CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 188762-12-1 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, pentahydrate, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



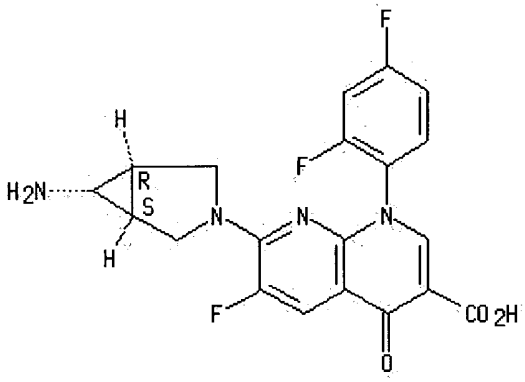
# 5 $H_2O$

IT **147059-75-4**, Trovafloxacin mesylate
RL: **RCT (Reactant)**; RACT (Reactant or reagent)
(prepn. of cryst. forms of trovafloxacin zwitterion)
RN 147059-75-4 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, (1α,5α,6α)-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

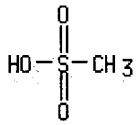
CRN 147059-72-1
CMF C20 H15 F3 N4 O3

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



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=> d his

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     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1                STRUCTURE UPLOADED
L2              0 S L1
L3              9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4              8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5                STRUCTURE UPLOADED
L6             10 S L5
L7            147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8             97 S L7/RCT
L9              2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10             0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11               STRUCTURE UPLOADED
L12             1 S L11
L13            21 S L11 FULL

     FILE 'HCAPLUS' ENTERED AT 12:23:44 ON 30 MAR 2004
L14           793 S L13
L15            27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
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                E METHANESULFONIC ACID
                E METHANESULFONIC ACID/CN
                E METHANESULFONIC ACID/CN
L16             1 S E3
L17               STRUCTURE UPLOADED
L18               STRUCTURE UPLOADED

     FILE 'HCAPLUS' ENTERED AT 12:33:37 ON 30 MAR 2004

     FILE 'REGISTRY' ENTERED AT 12:33:54 ON 30 MAR 2004
L19            44 S L17
L20            17 S L18 FULL
L21         15041 S L19 FULL

     FILE 'HCAPLUS' ENTERED AT 12:34:20 ON 30 MAR 2004
L22          2087 S L21/RCT
L23             5 S L22 AND L15

=> s l21 and l15
           19281 L21
L24           15 L21 AND L15

=> file caold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    30.86     850.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.47      -4.86

FILE 'CAOLD' ENTERED AT 12:36:03 ON 30 MAR 2004
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FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REG1stRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1                STRUCTURE UPLOADED
L2              0 S L1
L3              9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
```

```
L4             8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5               STRUCTURE UPLOADED
L6            10 S L5
L7           147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8            97 S L7/RCT
L9             2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10            0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11              STRUCTURE UPLOADED
L12            1 S L11
L13           21 S L11 FULL

     FILE 'HCAPLUS' ENTERED AT 12:23:44 ON 30 MAR 2004
L14          793 S L13
L15           27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
                E METHANESULFONIC ACID
                E METHANESULFONIC ACID/CN
                E METHANESULFONIC ACID/CN
L16            1 S E3
L17              STRUCTURE UPLOADED
L18              STRUCTURE UPLOADED

     FILE 'HCAPLUS' ENTERED AT 12:33:37 ON 30 MAR 2004

     FILE 'REGISTRY' ENTERED AT 12:33:54 ON 30 MAR 2004
L19           44 S L17
L20           17 S L18 FULL
L21        15041 S L19 FULL

     FILE 'HCAPLUS' ENTERED AT 12:34:20 ON 30 MAR 2004
L22         2087 S L21/RCT
L23            5 S L22 AND L15
L24           15 S L21 AND L15

     FILE 'CAOLD' ENTERED AT 12:36:03 ON 30 MAR 2004

=> s l21 and 15
      end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:n

=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1               STRUCTURE UPLOADED
L2             0 S L1
L3             9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
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L4             8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5               STRUCTURE UPLOADED
L6            10 S L5
L7           147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8            97 S L7/RCT
L9             2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10            0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11              STRUCTURE UPLOADED
L12            1 S L11
L13           21 S L11 FULL

     FILE 'HCAPLUS' ENTERED AT 12:23:44 ON 30 MAR 2004
L14          793 S L13
L15           27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
                E METHANESULFONIC ACID
                E METHANESULFONIC ACID/CN
                E METHANESULFONIC ACID/CN
L16            1 S E3
L17              STRUCTURE UPLOADED
L18              STRUCTURE UPLOADED

     FILE 'HCAPLUS' ENTERED AT 12:33:37 ON 30 MAR 2004

     FILE 'REGISTRY' ENTERED AT 12:33:54 ON 30 MAR 2004
L19           44 S L17
L20           17 S L18 FULL
L21        15041 S L19 FULL

     FILE 'HCAPLUS' ENTERED AT 12:34:20 ON 30 MAR 2004
L22         2087 S L21/RCT
L23            5 S L22 AND L15
L24           15 S L21 AND L15

     FILE 'CAOLD' ENTERED AT 12:36:03 ON 30 MAR 2004

=> s 21 and l15
QUALIFICATION NOT VALID FOR L13
Field code qualifications can only be applied to text
terms.

=> s l21 and l15
QUALIFICATION NOT VALID FOR L13
Field code qualifications can only be applied to text
terms.

=> s l13 and l21
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            604 L21
L25           0 L13 AND L21
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                                                          ENTRY    SESSION
FULL ESTIMATED COST                                         2.52     852.57

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CA SUBSCRIBER PRICE                                         0.00      -4.86

FILE 'REGISTRY' ENTERED AT 12:39:23 ON 30 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   29 MAR 2004  HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES:  29 MAR 2004  HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
L26     STRUCTURE UPLOADED

=> s 126
SAMPLE SEARCH INITIATED 12:39:53 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      7 TO ITERATE

100.0% PROCESSED       7 ITERATIONS                                 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            7 TO      298
PROJECTED ANSWERS:               0 TO        0

L27           0 SEA SSS SAM L26

=> s 126 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:39:58 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    163 TO ITERATE

100.0% PROCESSED     163 ITERATIONS                              17 ANSWERS
SEARCH TIME: 00.00.01

L28          17 SEA SSS FUL L26
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=> file hcaplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       155.42    1007.99

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -4.86

FILE 'HCAPLUS' ENTERED AT 12:40:02 ON 30 MAR 2004
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FILE COVERS 1907 - 30 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004  (20040329/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l28/prep
            14 L28
       3128003 PREP/RL
L29         11 L28/PREP
                 (L28 (L) PREP/RL)

=> s l29 and hydro?
       3744615 HYDRO?
L30         5 L29 AND HYDRO?

=> d his

     (FILE 'HOME' ENTERED AT 12:11:35 ON 30 MAR 2004)

     FILE 'REGISTRY' ENTERED AT 12:11:42 ON 30 MAR 2004
L1              STRUCTURE UPLOADED
L2            0 S L1
L3            9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4            8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5              STRUCTURE UPLOADED
L6           10 S L5
L7          147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
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L8            97 S L7/RCT
L9             2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10            0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11              STRUCTURE UPLOADED
L12            1 S L11
L13           21 S L11 FULL

     FILE 'HCAPLUS' ENTERED AT 12:23:44 ON 30 MAR 2004
L14          793 S L13
L15           27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
                E METHANESULFONIC ACID
                E METHANESULFONIC ACID/CN
                E METHANESULFONIC ACID/CN
L16            1 S E3
L17              STRUCTURE UPLOADED
L18              STRUCTURE UPLOADED

     FILE 'HCAPLUS' ENTERED AT 12:33:37 ON 30 MAR 2004

     FILE 'REGISTRY' ENTERED AT 12:33:54 ON 30 MAR 2004
L19           44 S L17
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L21        15041 S L19 FULL

     FILE 'HCAPLUS' ENTERED AT 12:34:20 ON 30 MAR 2004
L22         2087 S L21/RCT
L23            5 S L22 AND L15
L24           15 S L21 AND L15

     FILE 'CAOLD' ENTERED AT 12:36:03 ON 30 MAR 2004
L25            0 S L13 AND L21

     FILE 'REGISTRY' ENTERED AT 12:39:23 ON 30 MAR 2004
L26              STRUCTURE UPLOADED
L27            0 S L26
L28           17 S L26 FULL

     FILE 'HCAPLUS' ENTERED AT 12:40:02 ON 30 MAR 2004
L29           11 S L28/PREP
L30            5 S L29 AND HYDRO?

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L31           3 L30 NOT L23

=> d l31, ibib abs fhitstr, 1-3

L31  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:         1999:113705  HCAPLUS
DOCUMENT NUMBER:          130:168660
TITLE:                    Purification of alatrofloxacin parenteral compositions
                          and preparation of alatrofloxacin oligomer as
                          antibacterial agent
```

INVENTOR(S): Guinn, Robert Mark; Lambert, John Francis; Guhan, Subramanian Sam; Walinsky, Stanley Walter

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

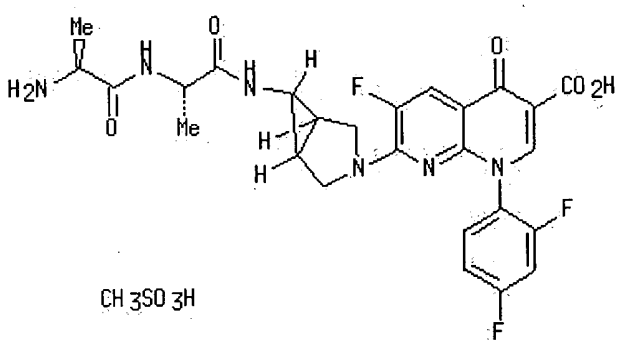
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9906430 | A1 | 19990211 | WO 1998-IB1122 | 19980723 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9882368 | A1 | 19990222 | AU 1998-82368 | 19980723 |
| AU 734863 | B2 | 20010621 | | |
| EP 1000086 | A1 | 20000517 | EP 1998-932444 | 19980723 |
| EP 1000086 | B1 | 20040218 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9811580 | A | 20000822 | BR 1998-11580 | 19980723 |
| JP 2001512133 | T2 | 20010821 | JP 2000-505185 | 19980723 |
| JP 3463928 | B2 | 20031105 | | |
| NZ 502249 | A | 20011130 | NZ 1998-502249 | 19980723 |
| CA 2296466 | C | 20030415 | CA 1998-2296466 | 19980723 |
| HR 980417 | B1 | 20021031 | HR 1998-980417 | 19980728 |
| AP 1031 | A | 20011221 | AP 1998-1310 | 19980730 |
| W: BW, GM, KE, MW, UG, ZM, ZW | | | | |
| ZA 9806874 | A | 20000131 | ZA 1998-6874 | 19980731 |
| US 6194429 | B1 | 20010227 | US 1999-403886 | 19991027 |
| NO 2000000485 | A | 20000327 | NO 2000-485 | 20000131 |
| MX 200001142 | A | 20001108 | MX 2000-1142 | 20000201 |

PRIORITY APPLN. INFO.: US 1997-54246P P 19970801
WO 1998-IB1122 W 19980723

GI




I

AB The present invention relates to alatrofloxacin mesylate (I) substantially

free of less polar impurities, to parenteral compns. of alatrofloxacin mesylate, and to processes for purifying alatrofloxacin mesylate. Thus, treatment of 50 g alatrofloxacin mesylate contg. approx. 700 ppm of an oligomer impurity in addn. to other less polar impurities, was dissolved on 0.05% aq. MeSO3H, and then Mitsubishi Diaion HP 20® **hydrophobic** resin (50 g) was added. After stirring the resin for 24 h in the dark, the slurry was filtered and the soln. analyzed by HPLC. The filtered soln. contained 19 ppm of the oligomer impurity with an 80% recovered yield of alatrofloxacin mesylate.

IT **220293-27-6P**

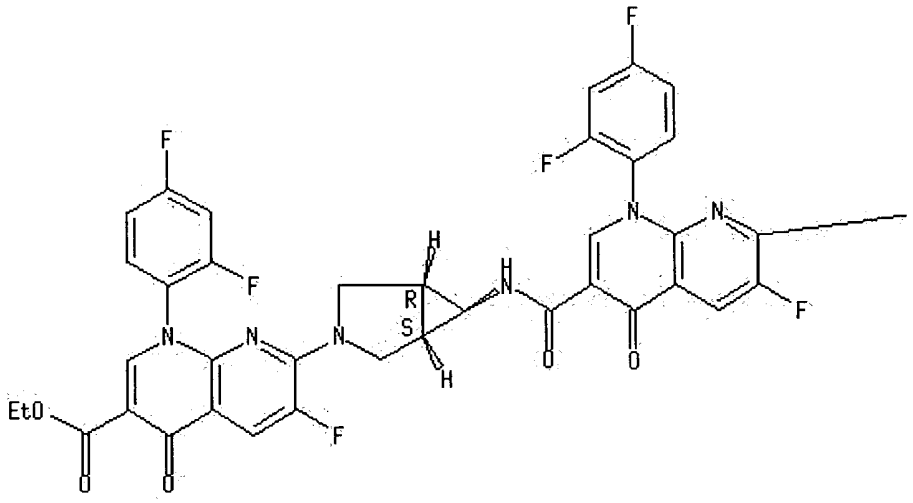
RL: RCT (Reactant); SPN (Synthetic preparation); **PREP (Preparation)**; RACT (Reactant or reagent)
(purifn. of alatrofloxacin parenteral compns. and prepn. of alatrofloxacin oligomer as antibacterial agent)

RN 220293-27-6 HCAPLUS

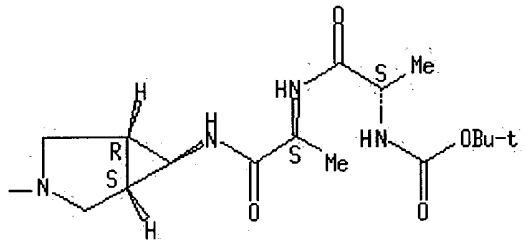
CN L-Alaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[(1α,5α,6α)-3-[8-(2,4-difluorophenyl)-6-[[[(1α,5α,6α)-3-[8-(2,4-difluorophenyl)-6-(ethoxycarbonyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]amino]carbonyl]-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1993:517227 HCAPLUS
DOCUMENT NUMBER: 119:117227
TITLE: Preparation of azabicycloalkylquinolones and -naphthyridinones as antibacterials
INVENTOR(S): Brighty, Katherine E.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 42 pp. Cont.-in-part of U.S. Ser. No. 551,212, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5164402 | A | 19921117 | US 1991-650835 | 19910204 |
| US 5229396 | A | 19930720 | US 1992-919477 | 19920724 |
| US 5266569 | A | 19931130 | US 1993-12202 | 19930202 |
| US 5391763 | A | 19950221 | US 1993-88999 | 19930826 |
| PRIORITY APPLN. INFO.: | | | US 1990-551212 | 19900711 |
| | | | US 1991-650835 | 19910204 |
| | | | US 1992-919477 | 19920724 |
| | | | US 1993-12202 | 19930202 |

OTHER SOURCE(S): MARPAT 119:117227
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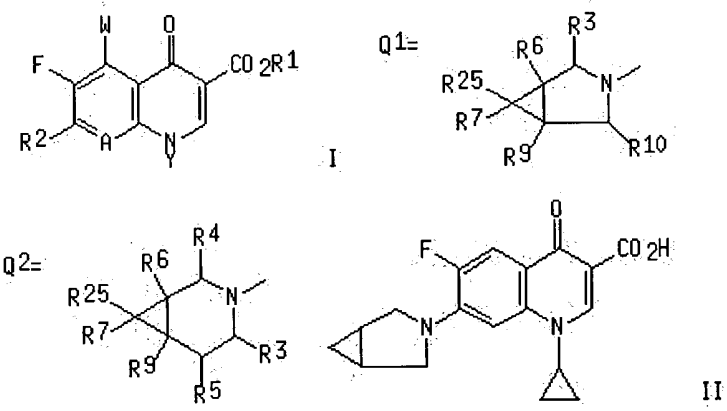
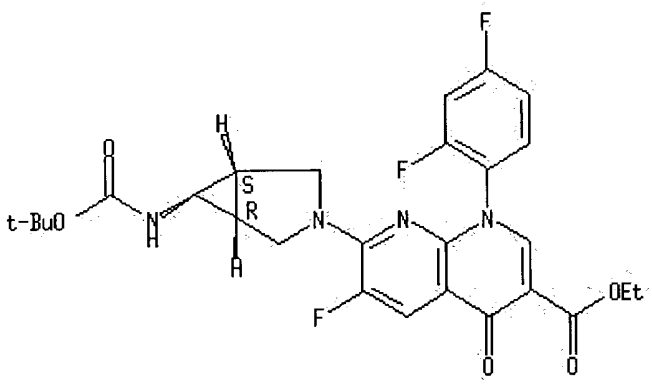



AB Title compds. [I; R1 = H, alkyl, pharmaceutically acceptable cation; Y = Et, Me3C, vinyl cyclopropyl, FCH2CH2, 4-FC6H4, 2,4-F2C6H34; W = F, Cl, Br, alkyl, alkoxy, (methyl)amino; A = CH, CCl, C(OMe), CMe, CCN, N; AY = atoms to form a (O-or double bond-contg.) (substituted) 5-6 membered ring; R2 = Q1, Q2; R3, R4, R5, R6, R7, R9 = H, Me, CH2NH2, CH2NHMe, CH2NHEt; R5, R6, R1, R9 may also = NH2, NHMe, NHEt; ≤3 of R3, R4, R6, R7, R9, R10, R25 ≠ H; if 3 of these ≠ H, ≥1 of them = Me], were prepd. as antibacterials (no data). Thus, 3-azabicyclo[3.1.0]hexane **hydrochloride** was heated with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinolinecarboxylic acid and Et3N in MgSO to give title compd. II.

IT **134575-66-9P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. of, as intermediate for antibacterial)

RN 134575-66-9 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]amino]-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.




L31 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

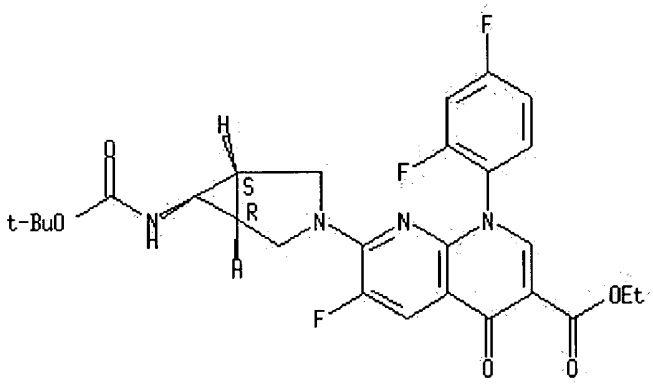
ACCESSION NUMBER: 1991:632216 HCAPLUS
DOCUMENT NUMBER: 115:232216
TITLE: Preparation of 7-(azabicycloalkyl)quinolone- and -naphthyridonecarboxylates as antibacterials
INVENTOR(S): Brighty, Katherine Elizabeth
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Eur. Pat. Appl., 73 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 413455 | A2 | 19910220 | EP 1990-308331 | 19900730 |
| EP 413455 | A3 | 19911009 | | |
| EP 413455 | B1 | 19950621 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| WO 9102526 | A1 | 19910307 | WO 1989-US3489 | 19890816 |
| W: FI, HU, NO, SU, US | | | | |
| HU 59919 | A2 | 19920728 | HU 1992-460 | 19890816 |
| HU 219403 | B | 20010428 | | |
| RU 2049777 | C1 | 19951210 | RU 1989-5011662 | 19890816 |
| ES 2074131 | T3 | 19950901 | ES 1990-308331 | 19900730 |
| IL 95331 | A1 | 19950731 | IL 1990-95331 | 19900809 |
| CA 2023217 | AA | 19910217 | CA 1990-2023217 | 19900814 |
| CA 2023217 | C | 19961210 | | |
| PL 166381 | B1 | 19950531 | PL 1990-286484 | 19900814 |
| AU 9061042 | A1 | 19910221 | AU 1990-61042 | 19900815 |
| AU 623801 | B2 | 19920521 | | |
| CN 1049501 | A | 19910227 | CN 1990-106794 | 19900815 |
| CN 1025192 | B | 19940629 | | |
| DD 298399 | A5 | 19920220 | DD 1990-343474 | 19900815 |
| ZA 9006450 | A | 19920325 | ZA 1990-6450 | 19900815 |

| | | | | | |
|---|---|---|---|---|---|
| JP 03086875 | A2 | 19910411 | JP 1990-216461 | | 19900816 |
| JP 07002734 | B4 | 19950118 | | | |
| CZ 281127 | B6 | 19960612 | CZ 1990-4027 | | 19900816 |
| NO 9200599 | A | 19920414 | NO 1992-599 | | 19920214 |
| JP 07149758 | A2 | 19950613 | JP 1994-157008 | | 19940708 |
| JP 08019099 | B4 | 19960228 | | | |
| FI 9604520 | A | 19961111 | FI 1996-4520 | | 19961111 |
| PRIORITY APPLN. INFO.: | | | WO 1989-US3489 | A | 19890816 |
| | | | FI 1992-632 | A | 19920214 |

OTHER SOURCE(S): MARPAT 115:232216
GI For diagram(s), see printed CA Issue.
AB Title compds. [I; R1 = H, alkyl, cation; Y = Et, Me3C, H2C:CH cyclopropyl, FCH2CH2, 4-FC6H4, 2,4-F2C6H3; W = H, F, Cl, Br, alkyl, alkoxy, amino, aminomethyl; A = CH, CF, CCl, COMe, CMe, CCN, N; AY = atoms to form a 5- or 6-membered ring, optionally contg. O or a double bond and optionally substituted by Me or :CH2; R2 = (Me-, H2NCH2-, MeNHCH2-, EtNHCH2-, etc. substituted) Q1, Q2], were prepd. as antibacterials (no data). Thus, a mixt. of 3-azabicyclo[3.1.0]hexane **hydrochloride**, 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, Et3N, and Me2SO was heated 18 h to give title compd. II.
IT **134575-66-9P**
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(prepn. of, as intermediate for (azabicycloalkyl)quinolone)
RN 134575-66-9 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 1-(2,4-difluorophenyl)-7-[6-[[(1,1-dimethylethoxy)carbonyl]amino]-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester, (1α,5α,6α)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

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FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)

  This file contains CAS Registry Numbers for easy and accurate
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  now searchable from 1907-1966.  TIFF images of CA abstracts
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L1              STRUCTURE UPLOADED
L2            0 S L1
L3            9 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 12:16:04 ON 30 MAR 2004
L4            8 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 12:16:10 ON 30 MAR 2004
L5              STRUCTURE UPLOADED
L6           10 S L5
L7          147 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 12:18:25 ON 30 MAR 2004
L8           97 S L7/RCT
L9            2 S L8 AND L4

     FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10           0 S L3 AND L7

     FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11             STRUCTURE UPLOADED
L12           1 S L11
L13          21 S L11 FULL

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L14         793 S L13
L15          27 S L13/PREP

     FILE 'REGISTRY' ENTERED AT 12:24:01 ON 30 MAR 2004
                E METHANESULFONIC ACID
                E METHANESULFONIC ACID/CN
                E METHANESULFONIC ACID/CN
L16           1 S E3
L17             STRUCTURE UPLOADED
L18             STRUCTURE UPLOADED

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     FILE 'REGISTRY' ENTERED AT 12:33:54 ON 30 MAR 2004
L19          44 S L17
L20          17 S L18 FULL
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L21        15041 S L19 FULL

     FILE 'HCAPLUS' ENTERED AT 12:34:20 ON 30 MAR 2004
L22         2087 S L21/RCT
L23            5 S L22 AND L15
L24           15 S L21 AND L15

     FILE 'CAOLD' ENTERED AT 12:36:03 ON 30 MAR 2004
L25            0 S L13 AND L21

     FILE 'REGISTRY' ENTERED AT 12:39:23 ON 30 MAR 2004
L26              STRUCTURE UPLOADED
L27            0 S L26
L28           17 S L26 FULL

     FILE 'HCAPLUS' ENTERED AT 12:40:02 ON 30 MAR 2004
L29           11 S L28/PREP
L30            5 S L29 AND HYDRO?
L31            3 S L30 NOT L23

     FILE 'CAOLD' ENTERED AT 12:41:13 ON 30 MAR 2004

=> s l28
L32            0 L28

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FULL ESTIMATED COST                                     0.42    1027.40

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CA SUBSCRIBER PRICE                                     0.00      -6.94

FILE 'REGISTRY' ENTERED AT 12:41:31 ON 30 MAR 2004
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STRUCTURE FILE UPDATES:   29 MAR 2004  HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES:  29 MAR 2004  HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L33      STRUCTURE UPLOADED
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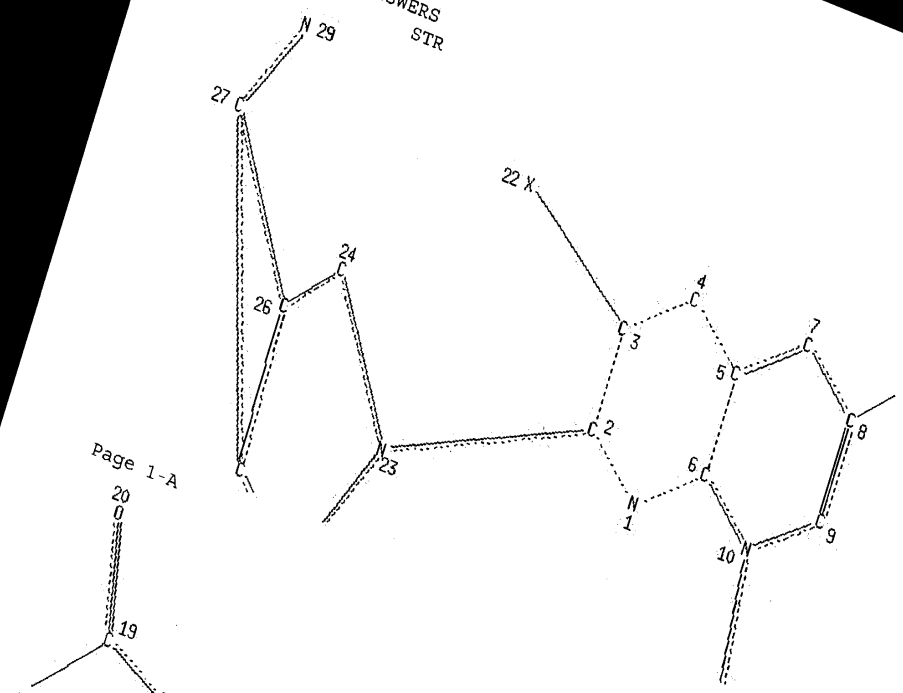
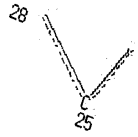
L33 HAS NO ANSWERS
L33 STR

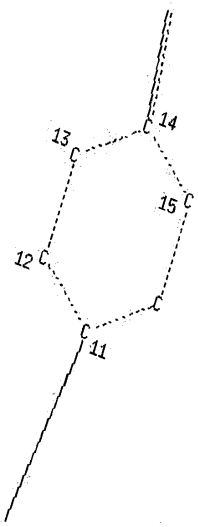



Page 1-A

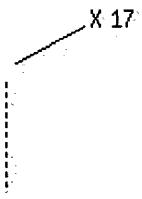



Page 1-B




Page 2-A

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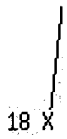


Page 3-A

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DEFAULT MLEVEL IS ATOM
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  29

STEREO ATTRIBUTES: NONE


=> s 133
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SAMPLE SCREEN SEARCH COMPLETED -      7 TO ITERATE
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100.0% PROCESSED       7 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            7 TO      298
PROJECTED ANSWERS:               3 TO      163

L34           3 SEA SSS SAM L33

=> s 133 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:43:01 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    163 TO ITERATE

100.0% PROCESSED     163 ITERATIONS                              75 ANSWERS
SEARCH TIME: 00.00.01

L35           75 SEA SSS FUL L33

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
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FULL ESTIMATED COST                             156.26    1183.66

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CA SUBSCRIBER PRICE                               0.00      -6.94

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FILE COVERS 1907 - 30 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004  (20040329/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l35
L36         811 L35

=> s l36 and chiu, c?/au
          1208 CHIU, C?/AU
L37          2 L36 AND CHIU, C?/AU
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=> d l37, ibib abs fhitstr, 1-2

L37 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:91540 HCAPLUS
DOCUMENT NUMBER: 134:147591
TITLE: Preparation of trovafloxacin
INVENTOR(S): **Chiu, Charles K.**; Wint, Lewin T.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6184380 | B1 | 20010206 | US 1999-236737 | 19990125 |
| US 2002095043 | A1 | 20020718 | US 2002-87756 | 20020304 |

PRIORITY APPLN. INFO.: US 1998-71601P P 19980116
US 1999-236737 A3 19990125
US 2000-718324 A3 20001122

OTHER SOURCE(S): CASREACT 134:147591; MARPAT 134:147591
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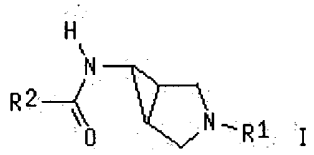


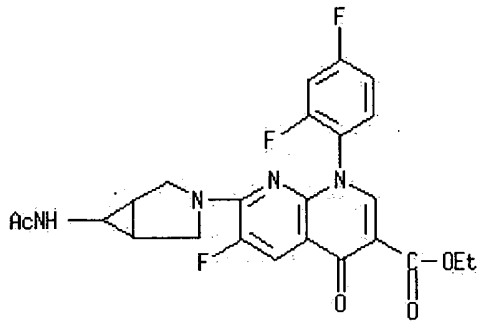
I

AB The title process comprises use of azabicyclohexanes I [R1 = (un)substituted CH2Ph; R2 = CF3, alkyl, (un)substituted Ph] and a 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid alkyl ester.

IT **323575-31-1P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of trovafloxacin)

RN 323575-31-1 HCAPLUS

CN 1,8-Naphthyridine-3-carboxylic acid, 7-[6-(acetylamino)-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)




REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:460272 HCAPLUS
DOCUMENT NUMBER: 131:116223
TITLE: Process for preparing naphthyridones and intermediates
INVENTOR(S): **Chiu, Charles Kwok-Fung**; Wint, Lewin Theophilus
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 930297 | A1 | 19990721 | EP 1999-300183 | 19990112 |
| EP 930297 | B1 | 20030423 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AU 9897115 | A1 | 19990805 | AU 1998-97115 | 19981215 |
| JP 11255745 | A2 | 19990921 | JP 1999-5494 | 19990112 |
| SG 76584 | A1 | 20001121 | SG 1999-46 | 19990112 |
| EG 21514 | A | 20011128 | EG 1999-34 | 19990112 |
| TW 483890 | B | 20020421 | TW 1999-88100415 | 19990112 |
| AT 238281 | E | 20030515 | AT 1999-300183 | 19990112 |
| ES 2195513 | T3 | 20031201 | ES 1999-300183 | 19990112 |
| BR 9900066 | A | 20000509 | BR 1999-66 | 19990114 |
| CA 2258960 | C | 20020903 | CA 1999-2258960 | 19990114 |
| CA 2258960 | AA | 19990716 | | |
| NO 9900185 | A | 19990719 | NO 1999-185 | 19990115 |
| CN 1228422 | A | 19990915 | CN 1999-101086 | 19990115 |
| NZ 333769 | A | 20000327 | NZ 1999-333769 | 19990115 |
| ZA 9900277 | A | 20000717 | ZA 1999-277 | 19990115 |
| BG 64094 | B1 | 20031231 | BG 1999-103087 | 19990115 |

PRIORITY APPLN. INFO.: US 1998-71601P P 19980116
OTHER SOURCE(S): CASREACT 131:116223; MARPAT 131:116223
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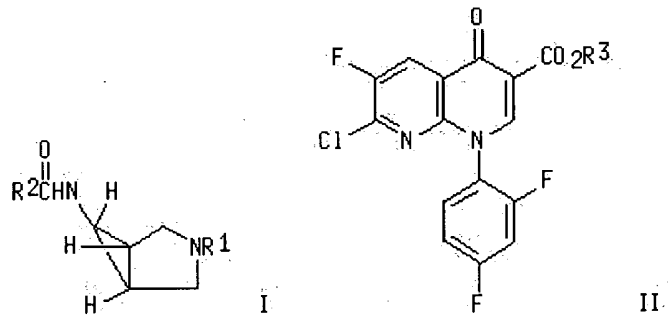


I II

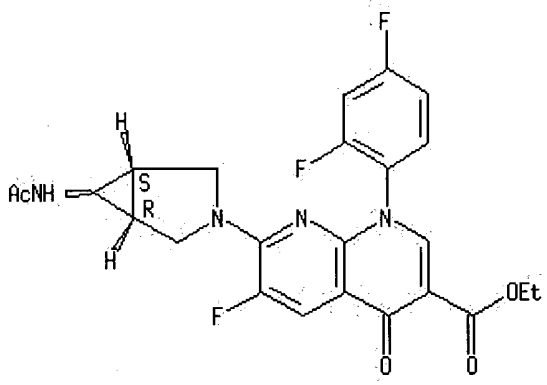
AB 6-Acetamido-3-benzylazabicyclo[3.1.0]hexanes [I; R1 = (un)substituted PhCH2; R2 = C1-6 alkyl, CF3, (un)substituted Ph] are prepd. by redn. of the parent nitro derivs. with Fe powder in AcOH/Me2CHOH and N-acylation of the resulting amines. Debenzylation of I with H in AcOH in the presence of Pd catalyst, condensation of debenzylated intermediates with naphthyridine-3-carboxylate esters (II; R3 = C1-6 alkyl) and hydrolysis of the resulting intermediates (prepn. procedure claimed) with MeSO3H in aq. org. solvents gives trovafloxacin (III), an antibacterial active esp. against gram-pos. bacterial strains, as monomethanesulfonate salt. Thus, III·HO3SMe was prepd. from I (R1 = PhCH2, R2 = Me) and II (R3 = Et) as described above.

IT **232598-25-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrolysis with methanesulfonic acid; process for prepg. naphthyridones and trovafloxacin intermediates)

RN 232598-25-3 HCAPLUS

CN 1,8-Naphthyridine-3-carboxylic acid, 7-[(1α,5α,6α)-6-(acetylamino)-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> fil USPATFULL;s (US 1998-71601P)/pn,apps

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| FULL ESTIMATED COST | 21.31 | 1204.97 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
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| CA SUBSCRIBER PRICE | -1.39 | -8.33 |

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CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 30 Mar 2004 (20040330/PD)
FILE LAST UPDATED: 30 Mar 2004 (20040330/ED)
HIGHEST GRANTED PATENT NUMBER: US6715148
HIGHEST APPLICATION PUBLICATION NUMBER: US2004060089
CA INDEXING IS CURRENT THROUGH 30 Mar 2004 (20040330/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 30 Mar 2004 (20040330/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2004

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>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
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>>>                                                                    <<<
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>>>  classifications, or claims, that may potentially change from     <<<
>>>  the earliest to the latest publication.                           <<<

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                (US98071601/PN)
            0 US98-71601P/AP
            2 US98-71601P/PRN
            0 US98-71601P/RLN
            2 (US 1998-71601P)/APPS
                (US98-71601P/AP,PRN,RLN)
L38         2 (US 1998-71601P)/PN,APPS

=> d 1 iallg

L38  ANSWER 1 OF 2  USPATFULL on STN
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ACCESSION NUMBER:         2002:179251  USPATFULL
TITLE:                    Process for preparing naphthyridones and intermediates
INVENTOR(S):              Chiu, Charles K., New York, NY, UNITED STATES
                          Wint, Lewin T., New York, NY, UNITED STATES

                               NUMBER         KIND    DATE
                          ---------------- ------ --------
PATENT INFORMATION:       US 2002095043      A1   20020718
APPLICATION INFO.:        US 2002-87756      A1   20020304  (10)
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RELATED APPLN. INFO.: Division of Ser. No. US 2000-718324, filed on 22 Nov 2000, PENDING Division of Ser. No. US 1999-236737, filed on 25 Jan 1999, GRANTED, Pat. No. US 6184380

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 1998-71601P | 19980116 (60) | <-- |
| DOCUMENT TYPE: | Utility | | |
| FILE SEGMENT: | APPLICATION | | |
| LEGAL REPRESENTATIVE: | Paul H. Ginsburg, Pfizer Inc., 235 East 42nd Street, 20th Floor, New York, NY, 10017-5755 | | |
| NUMBER OF CLAIMS: | 12 | | |
| EXEMPLARY CLAIM: | 1 | | |

ABSTRACT:

A process for preparing a naphthyridone carboxylic acid and its derivatives makes use of side chain intermediates of formulae I and IV herein.

[0001] This invention relates to a process for preparing the naphthyridone carboxylic acid, trovafloxacin and derivatives thereof, and intermediates of use therein.

[0002] Trovafloxacin has the formula ##STR1##

[0003] as disclosed in U.S. Pat. No. 5,164,402. The patent also discloses processes for making the compound by using an intermediate of the formula ##STR2##

[0004] wherein R' is a nitrogen protecting group, such as tertiary butyloxycarbonyl.

[0005] U.S. Pat. No. 5,475,116 discloses the preparation of other intermediates for use in preparing the naphthyridones of U.S. Pat. No. 5,164,402.

[0006] The present invention relates to a process for preparing a compound of the formula ##STR3##

[0007] wherein $R^1$ is benzyl, wherein the phenyl of the benzyl may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, and

[0008] $R^2$ is $C_{1-C6}$ alky, trifluoromethyl, or phenyl which may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, which comprises

[0009] (a) reducing a compound of the formula ##STR4##

[0010] wherein $R^1$ is as defined above, in the presence of iron and a organic solvent under acidic conditions, and

[0011] (b) acylating the compound of formula III formed: ##STR5##

[0012] with an acylating agent of the formula $R^{2C}(O)X$ wherein $R^2$ is as defined above, and X is a leaving group.

[0013] In a prefered embodiment of the invention, the compound of formula III formed in step (a) is not isolated before acylation step (b).

[0014] The invention is further related to a process for preparing a compound

of the formula ##STR6##

[0015] by debenzylating the compound of formula I wherein $R^1$ and $R^2$ are as defined above.

[0016] In a preferred embodiment, the debenzylation is carried out by reacting a compound of formula I with hydrogen and palladium catalyst in acetic acid and an organic solvent.

[0017] The invention also relates to reacting a compound of the formula IV with a compound of the formula ##STR7##

[0018] wherein $R^3$ is $C_{1-C6}$ alkyl, to form a compound of the formula ##STR8##

[0019] wherein $R^2$ is as defined above with reference to formula I.

[0020] The invention relates to hydrolyzing the compound of formula VI with methanesulfonic acid, water and an organic solvent to form the monomethanesulfonic acid salt of the compound of the formula VII, trovafloxacin.

[0021] The invention also relates to hydrolysis of the compound of formula VI with methanesulfonic acid and $R^{3OH}$ wherein $R^3$ is as defined above to form the monomethanesulfonic acid salt of the compound of the formula ##STR9##

[0022] The invention further relates to the intermediates of the formulae ##STR10##

[0023] wherein $R^2$ is $C_{1-C6}$ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, and $R^3$ is $C_{1-C6}$ alkyl, and ##STR11##

[0024] wherein

[0025] $R^1$ is hydrogen (see formula IV) or benzyl, wherein the phenyl of the benzyl may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, and

[0026] $R^2$ is $C_{1-C6}$ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl.

[0027] The term "alkyl", as used herein, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties, e.g. methyl, ethyl.

[0028] The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

[0029] The processes of the invention are depicted in the following reaction scheme. Unless indicated otherwise, $R^1$ $R^2$, $R^3$ and X are as defined above. ##STR12##

[0030] The compound of formula III is prepared from the corresponding compound of formula II by reduction in the presence of iron and an organic solvent under

acidic conditions. The organic solvent is a $C_{1-C6}$ alcohol, such as ethanol, or an ether such as tetrahydrofuran (THF), and preferably, an alcohol. The acidic conditions are obtained by use of a mineral acid, such as hydrochloric acid, or an organic acid, such as acetic acid (AcOH). Acetic acid is preferred since it generally results in increased yields.

[0031] The compound of formula III may then be isolated from the reaction mixture or may be reacted further in situ, without isolation from the reaction mixture. In either case, the further processing is by acylation with an acylating agent of the formula $R^{2C}(O)X$ to form the compound of formula I. The leaving group X is conveniently a halogen, such as chloro, or the acetoxy group. If the compound of formula III is first isolated, then the acylation may be conducted under conventional acylating conditions, for instance, in the presence of an organic solvent of the type discussed above.

[0032] The compound of formula I is subjected to debenzylation to form the compound of formula IV. It is understood that in the context of the invention, debenzylation includes removal of $R^1$ wherein $R^1$ is benzyl or substituted benzyl. The reaction proceeds in accordance with conventional debenzylation of tertiary nitrogen, conveniently by use of hydrogen and palladium catalyst in acetic acid, and in an organic solvent. The organic solvent may be a $C_{1-C6}$ alcoholic solvent, such as ethanol, ethyl acetate, THF or water, or a mixture thereof, such as ethanol and water.

[0033] The compound of formula VI is obtained by coupling the corresponding compound of formula IV with the bicyclic intermediate ester of formula V. This coupling reaction may be conducted with or without a solvent. The solvent, when used, must be inert under the reaction conditions. Suitable solvents are ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, chloroform, dimethylsulfoxide, pyridine, and water, and mixtures thereof.

[0034] The reaction temperature usually ranges from about 20° C. to about 150° C.

[0035] The reaction may advantageously be carried out in the presence of an acid acceptor such as an inorganic or organic base, e.g. an alkali metal or alkaline earth metal carbonate or bicarbonate, or a tertiary amine, e.g. triethylamine, pyridine or picoline.

[0036] The mesylate salt of the compound of formula VII, trovafloxacin, is formed by hydrolysis of the compound of formula VI with methanesulfonic acid, water and an organic solvent. Examples of suitable organic solvents include a $C_{1-C6}$ alcohol, acetone, dimethoxy ethane, glyme, THF, N-methyl-pyrrolidinone, and water, and mixtures thereof.

[0037] The mesylate salt of the compound of formula VIII is obtained by hydrolysis of the compound of formula VI with methanesulfonic acid and a $C_{1-C6}$ alcohol of the formula $R^{3OH}$, for example ethanol. The compound of formula VIII is an intermediate in the preparation of the mesylate salt of a prodrug of trovafloxacin wherein the amino group is substituted by an amino acid or a polypeptide, e.g. dipeptide, as disclosed in U.S. Pat. No. 5,164,402.

[0038] The compound of formula IX in the Reaction Scheme is the intermediate formed in the reaction from compound VI to VII.

[0039] The compound of formula VII and the mesylate salt thereof (the active compounds) are useful in the treatment of bacterial infections of broad spectrum, particularly the treatment of gram-positive bacterial strains.

[0040] The active compounds may be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally or in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25-500 ppm. They can be injected parenterally, for example, intramuscularly, intravenously or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which can contain other solutes, for example, enough salt or flucose to make the solution isotonic. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1-50 mg/kg/day, advantageously 0.2-10 mg/kg/day given in a single daily dose or up to 3 divided doses.

[0041] The invention also provides pharmaceutical compositions comprising an antibacterially effective amount of a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier.

[0042] The compounds of the invention can be administered to humans for the treatment of bacterial diseases by either the oral or parenteral routes, and may be administered orally at dosage levels of about 0.1 to 500 mg/kg/day, advantageously 0.5-50 mg/kg/day given in a single dose or up to 3 divided doses. For intramuscular or intravenous administration, dosage levels are about 0.1-200 mg/kg/day, advantageously 0.5-50 mg/kg/day. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. Variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of administration chosen as will be known to those skilled in the art

[0043] The following Examples illustrate the invention. The abbreviations used mean the following: GC=gas chromatography; MS=mass spectometry; TLC=thin layer chromatography, HPLC=high performance liquid chromatography; LCMS=liquid chromatography mass spectometry; and NMR=nuclear magnetic resonance.

EXAMPLE 1

(1α, 5α, 6α)-6-Acetamido-3-benzyl-3-azabicyclo[3.1.0]hexane

[0044] A 3-necked round bottom flask, equiped with a thermometer, a overhead stirrer and a condenser with nitrogen purge, was charged with 768 g of nitrocyclopropane, 5.75 L of isopropanol (7.5 volumes), 1.79 L of acetic acid (9.1 equivalents) and 1153 g of iron powder (6 equivalents). The reaction mixture was heated at 50° C. until the reaction was completed by GC/MS analysis (about 6 hours). 448 mL of acetic anhydride (1.4 equivalents) was added and stirred at 50° C. for 15 minutes before cooling. The reaction mixture was diluted with 8 L isopropanol (10.5 volumes) and stirred for 30 minutes. The residual iron was filtered off and the cake washed with 11.25 L of isopropanol (15 volumes). The isopropanol solution was concentrated in vacuo to an oil, 18 L of dichloroethane (24 volumes) was added before bringing the pH to 12 with 8.8 L of 5% sodium hydroxide solution (about 12 volumes). The layers were separated and the separated organic layer was dried by magnesium sulfate. The resulting dark amber oil was treated with 7.5 L of hexanes (10 volumes) and granulated at 25° C. before collecting the product as a white solid. Drying at 50° C. under vacuum gave 610 g of the title compound (77% yield). Analysis was done by GC/MS, NMR and TLC.

EXAMPLE 2

(1α, 5α, 6α)-6-Acetamido-3-azabicyclo[3.1.0]hexane

[0045] A Parr Bottle was charged with 150 g of the compound of Example 1, 112 mL of acetic acid (3 equivalents), 1.5 L of methanol (10 volumes) and 15 g of (10% by wt. 50% wet) Pd/C catalyst (0.1 equivalent). The bottle was purged with nitrogen and then brought to 50 psi pressure with hydrogen. The mixture was shaken for 48 hours and recharged with catalyst as necessary during the debenzylation reaction. After TLC indicated that the reaction was complete, the catalyst was filtered off, and the filtrate was concentrated in vacuo to an oil. 3 L of ethyl acetate (20 volumes) was added to the oil, and granulated for an hour. The solid was collected by filtration and dried under vacuum at 50° C. to provide 107 g of the title compound (82% yield) as the acetic acid salt

EXAMPLE 3

(1α, 5α, 6α)-7-(6-acetamido-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro4-oxo-1,8-naphthyridine-3-carboxylic Acid, Ethyl Ester

[0046] A reaction flask was charged with 241.9 g of 7-chloro-6-fluoro-1,4-dihydro4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester, 151.6 g of the acetic acid salt of the compound of Example 2 (1.2 equivalents), 2661 mL of ethyl acetate (11 volumes) and 220 mL of triethylamine (2.5 equivalents). The mixture was heated at refluxing temperature under nitrogen for 6 hours monitored by HPLC or LCMS. After the reaction was completed, the reaction mixture was cooled to ambient temperature. Water (11 volumes) was added and the biphasic mixture was stirred for 17 hours. The white solid was collected by filtration, washed with 2661 mL of water (12 volumes) and oven dried at 50° C. to provide 292 g of the title compound (95% yield).

EXAMPLE 4

[0047] In a reaction flask, 220 g of the compound of Example 3, 1.76 L of n-butanol (8 volumes), 1.54 L of water (7 volumes) and 141 mL of 70% methanesulfonic acid (3.0 equivalents) were mixed. The mixture was heated at reflux for 21 hours, and the reaction was monitored by HPLC or LCMS. After complete reaction, the mixture was cooled to 50° C. and filtered to make it speck-free. The filtrated was cooled to 0-5° C. and granulated for 2 hours. The solid was collected by filtration, washed with 220 mL of water (1 volume) and 660 mL n-butanol (3 volumes). The wet cake was mixed with 660 mL of n-butanol (3 volumes), seeded with 0.1 gm of the desired polymorph and heated to 95-100° C. After complete polymorph conversion, in approximately 2 hours, the mixture was cooled to ambient temperature. The solid was filtered, washed with 100 mL of n-butanol (0.5 volumes) and dried in a nitrogen atmosphere to provide 200 g of (1α, 5α, 6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate (87% yield).

EXAMPLE 5

[0048] 0.8 mL of methanesulfonic acid (2.7 equivalents) was added dropwise to a solution of 2.2 g of the compound of Example 3 in 10 mL of ethanol (4.5 volumes). The resulting reaction mixture was heated at refluxing temperature for 40 hours, monitored by GCMS. After the reaction was completed, it was diluted with ethyl acetate (20 mL) and washed with (3x 10 ml) 1M sodium

hydroxide solution. The organic layer was separated, dried over anhydrous magnesium sulphate and filtered. The filtrate was concentrated in vacuo to provide 1.37 g of (1α, 5α, 6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester, monomethanesulfonate (96% yield).

What is claimed is:

1. A process for preparing a compound of the formula ##STR13## wherein $R^1$ is benzyl, wherein the phenyl of the benzyl may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or tifluoromethyl, and $R^2$ is $C_{1-C6}$ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, which comprises (a) reducing a compound of the formula ##STR14## wherein $R^1$ is as defined above, in the presence of iron and a organic solvent under acidic conditions, and (b) acylating the compound of formula III formed: ##STR15## with an acylating agent of the formula $R^{2C}(O)X$ wherein $R^2$ is as defined above, and X is a leaving group.

2. A process according to claim 1 wherein the compound of the formula III formed in step (a) is not isolated before acylation step (b).

3. A process according to claim 1 or 2 wherein the compound of formula I wherein $R^1$ is as defined in claim 1, is subjected to debenzylation to form the compound of the formula ##STR16##

4. A process according to claim 3 wherein the debenzylation is by reaction with hydrogen and palladium catalyst in acetic acid and an organic solvent.

5. A process according to claim 3 or 4 further comprising reacting the compound of formula IV with a compound of the formula ##STR17## wherein $R^3$ is $C_{1-C6}$ alkyl, to form a compound of the formula ##STR18## wherein $R^2$ is as defined in claim 1

6. A process according to claim 5 further comprising hydrolysis of the compound of formula VI with methanesulfonic acid, water and an organic solvent to form the monomethanesulfonic acid salt of the compound of the formula ##STR19##

7. A process according to claim 5 or 6 further comprising hydrolysis of the compound of formula VI with methanesulfonic acid and $R^{3OH}$ wherein $R^3$ is as defined in claim 5 to form the monomethanesulfonic acid salt of the compound of the formula ##STR20##

8. A process for the preparation of a compound of the formula ##STR21## wherein $R^2$ is $R^2$ is $C_{1-C6}$ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, and $R^3$ is $C_{1-C6}$ alkyl, which comprises reacting a compound of the formula ##STR22## with a compound of the formula ##STR23##

9. A process according to claim 8, further comprising hydrolysis of the compound of formula VI with methanesulfonic acid, water and an organic solvent to form the monomethanesulfonic acid salt of the compound of the formula ##STR24##

10. A process according to claim 8, further comprising hydrolysis of the

compound of formula VI with methanesulfonic acid and $R^{3OH}$ wherein $R^3$ is as defined in claim 5 to form the monomethanesulfonic acid salt of the compound of the formula ##STR25##

11. A compound of the formula ##STR26## wherein $R^2$ is $C_{1-C6}$ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, and $R^3$ is $C_{1-C6}$ alkyl.

12. A compound of the formula ##STR27## wherein $R^1$ is hydrogen or benzyl, wherein the phenyl of the benzyl may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl, and $R^2$ is $C_{1-C6}$ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of $C_{1-C6}$ alkyl, $C_{1-C6}$ alkoxy, halo, nitro, amino or trifluoromethyl.

ISSUE U.S. PATENT CLASSIF.:
MAIN: 548/452.000
CURRENT U.S. PATENT CLASSIF.:
MAIN: 548/452.000
INT. PATENT CLASSIF.: [7]
MAIN: C07D209-02
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> **file reg**

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| FULL ESTIMATED COST | 5.45 | 1210.42 |

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FILE COVERS 1907 - 30 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004 (20040329/ED)

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L3 9 S L1 FULL

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L4 8 S L3/PREP

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L5 STRUCTURE UPLOADED
L6 10 S L5
L7 147 S L5 FULL

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L8 97 S L7/RCT
L9 2 S L8 AND L4

FILE 'CAOLD' ENTERED AT 12:19:48 ON 30 MAR 2004
L10 0 S L3 AND L7

FILE 'REGISTRY' ENTERED AT 12:20:07 ON 30 MAR 2004
L11 STRUCTURE UPLOADED
L12 1 S L11
L13 21 S L11 FULL

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L15           27 S L13/PREP

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L22         2087 S L21/RCT
L23            5 S L22 AND L15
L24           15 S L21 AND L15

     FILE 'CAOLD' ENTERED AT 12:36:03 ON 30 MAR 2004
L25            0 S L13 AND L21

     FILE 'REGISTRY' ENTERED AT 12:39:23 ON 30 MAR 2004
L26              STRUCTURE UPLOADED
L27            0 S L26
L28           17 S L26 FULL

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L31            3 S L30 NOT L23

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L38            2 S (US 1998-71601P)/PN,APPS

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DICTIONARY FILE UPDATES:  29 MAR 2004  HIGHEST RN 668968-88-5

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L41 HAS NO ANSWERS
L41              STR

=> s l41
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100.0% PROCESSED       2 ITERATIONS                              0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             2 TO      124
PROJECTED ANSWERS:                0 TO        0
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L42             0 SEA SSS SAM L41

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THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 12:49:24 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      37 TO ITERATE

100.0% PROCESSED       37 ITERATIONS                                5 ANSWERS
SEARCH TIME: 00.00.01

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                   156.26    1369.46

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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FILE COVERS 1907 - 30 Mar 2004  VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004  (20040329/ED)

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L44             4 L43

=> d l44, ibib abs fhitstr, 1-4

L44  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

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ACCESSION NUMBER:         2001:91540  HCAPLUS
DOCUMENT NUMBER:          134:147591
TITLE:                    Preparation of trovafloxacin
INVENTOR(S):              Chiu, Charles K.; Wint, Lewin T.
PATENT ASSIGNEE(S):       Pfizer Inc., USA
SOURCE:                   U.S., 7 pp.
                          CODEN: USXXAM
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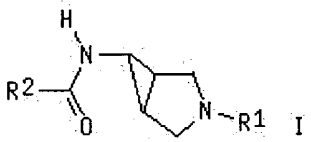
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

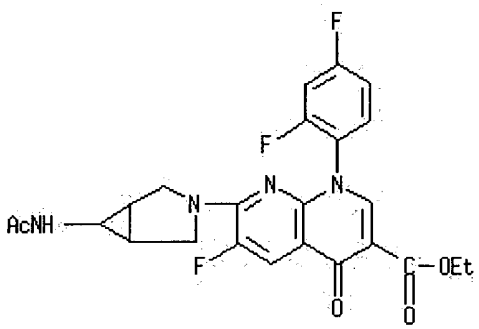
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6184380 | B1 | 20010206 | US 1999-236737 | 19990125 |
| US 2002095043 | A1 | 20020718 | US 2002-87756 | 20020304 |

PRIORITY APPLN. INFO.: US 1998-71601P P 19980116
US 1999-236737 A3 19990125
US 2000-718324 A3 20001122
OTHER SOURCE(S): CASREACT 134:147591; MARPAT 134:147591
GI



I

AB The title process comprises use of azabicyclohexanes I [R1 = (un)substituted CH2Ph; R2 = CF3, alkyl, (un)substituted Ph] and a 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid alkyl ester.
IT **323575-31-1P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of trovafloxacin)
RN 323575-31-1 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-[6-(acetylamino)-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:460272 HCAPLUS
DOCUMENT NUMBER: 131:116223
TITLE: Process for preparing naphthyridones and intermediates
INVENTOR(S): Chiu, Charles Kwok-Fung; Wint, Lewin Theophilus
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 930297 | A1 | 19990721 | EP 1999-300183 | 19990112 |
| EP 930297 | B1 | 20030423 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| AU 9897115 | A1 | 19990805 | AU 1998-97115 | 19981215 |
| JP 11255745 | A2 | 19990921 | JP 1999-5494 | 19990112 |
| SG 76584 | A1 | 20001121 | SG 1999-46 | 19990112 |
| EG 21514 | A | 20011128 | EG 1999-34 | 19990112 |
| TW 483890 | B | 20020421 | TW 1999-88100415 | 19990112 |
| AT 238281 | E | 20030515 | AT 1999-300183 | 19990112 |
| ES 2195513 | T3 | 20031201 | ES 1999-300183 | 19990112 |
| BR 9900066 | A | 20000509 | BR 1999-66 | 19990114 |
| CA 2258960 | C | 20020903 | CA 1999-2258960 | 19990114 |
| CA 2258960 | AA | 19990716 | | |
| NO 9900185 | A | 19990719 | NO 1999-185 | 19990115 |
| CN 1228422 | A | 19990915 | CN 1999-101086 | 19990115 |
| NZ 333769 | A | 20000327 | NZ 1999-333769 | 19990115 |
| ZA 9900277 | A | 20000717 | ZA 1999-277 | 19990115 |
| BG 64094 | B1 | 20031231 | BG 1999-103087 | 19990115 |

PRIORITY APPLN. INFO.: US 1998-71601P P 19980116
OTHER SOURCE(S): CASREACT 131:116223; MARPAT 131:116223
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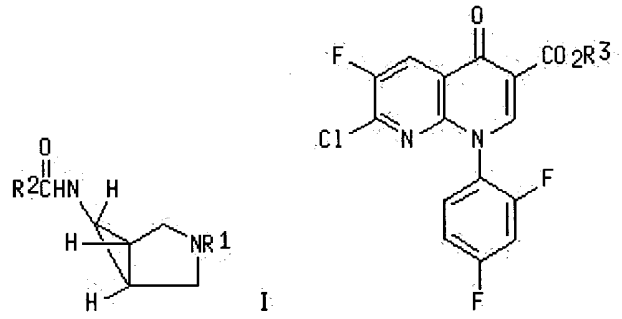


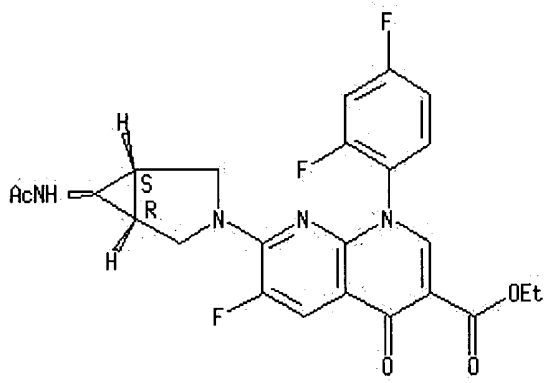

I II

AB 6-Acetamido-3-benzylazabicyclo[3.1.0]hexanes [I; R1 = (un)substituted PhCH2; R2 = C1-6 alkyl, CF3, (un)substituted Ph] are prepd. by redn. of the parent nitro derivs. with Fe powder in AcOH/Me2CHOH and N-acylation of the resulting amines. Debenzylation of I with H in AcOH in the presence of Pd catalyst, condensation of debenzylated intermediates with naphthyridine-3-carboxylate esters (II; R3 = C1-6 alkyl) and hydrolysis of the resulting intermediates (prepn. procedure claimed) with MeSO3H in aq. org. solvents gives trovafloxacin (III), an antibacterial active esp. against gram-pos. bacterial strains, as monomethanesulfonate salt. Thus, III·HO3SMe was prepd. from I (R1 = PhCH2, R2 = Me) and II (R3 = Et) as described above.

IT **232598-25-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrolysis with methanesulfonic acid; process for prepg.

naphthyridones and trovafloxacin intermediates)
RN 232598-25-3 HCAPLUS
CN 1,8-Naphthyridine-3-carboxylic acid, 7-[(1α,5α,6α)-6-(acetylamino)-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)

Relative stereochemistry.




REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:113705 HCAPLUS
DOCUMENT NUMBER: 130:168660
TITLE: Purification of alatrofloxacin parenteral compositions and preparation of alatrofloxacin oligomer as antibacterial agent
INVENTOR(S): Guinn, Robert Mark; Lambert, John Francis; Guhan, Subramanian Sam; Walinsky, Stanley Walter
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9906430 | A1 | 19990211 | WO 1998-IB1122 | 19980723 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9882368 | A1 | 19990222 | AU 1998-82368 | 19980723 |
| AU 734863 | B2 | 20010621 | | |
| EP 1000086 | A1 | 20000517 | EP 1998-932444 | 19980723 |
| EP 1000086 | B1 | 20040218 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9811580 | A | 20000822 | BR 1998-11580 | 19980723 |

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|---|---|---|---|---|---|
| JP 2001512133 | T2 | 20010821 | JP 2000-505185 | | 19980723 |
| JP 3463928 | B2 | 20031105 | | | |
| NZ 502249 | A | 20011130 | NZ 1998-502249 | | 19980723 |
| CA 2296466 | C | 20030415 | CA 1998-2296466 | | 19980723 |
| HR 980417 | B1 | 20021031 | HR 1998-980417 | | 19980728 |
| AP 1031 | A | 20011221 | AP 1998-1310 | | 19980730 |
| W: BW, GM, KE, MW, UG, ZM, ZW | | | | | |
| ZA 9806874 | A | 20000131 | ZA 1998-6874 | | 19980731 |
| US 6194429 | B1 | 20010227 | US 1999-403886 | | 19991027 |
| NO 2000000485 | A | 20000327 | NO 2000-485 | | 20000131 |
| MX 200001142 | A | 20001108 | MX 2000-1142 | | 20000201 |
| PRIORITY APPLN. INFO.: | | | US 1997-54246P | P | 19970801 |
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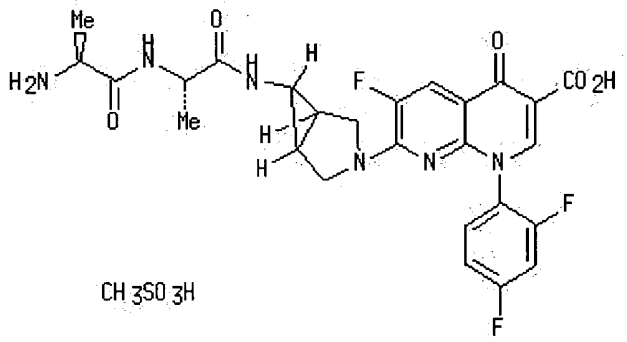



I

AB The present invention relates to alatrofloxacin mesylate (I) substantially free of less polar impurities, to parenteral compns. of alatrofloxacin mesylate, and to processes for purifying alatrofloxacin mesylate. Thus, treatment of 50 g alatrofloxacin mesylate contg. approx. 700 ppm of an oligomer impurity in addn. to other less polar impurities, was dissolved on 0.05% aq. MeSO3H, and then Mitsubishi Diaion HP 20® hydrophobic resin (50 g) was added. After stirring the resin for 24 h in the dark, the slurry was filtered and the soln. analyzed by HPLC. The filtered soln. contained 19 ppm of the oligomer impurity with an 80% recovered yield of alatrofloxacin mesylate.

IT **220293-27-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

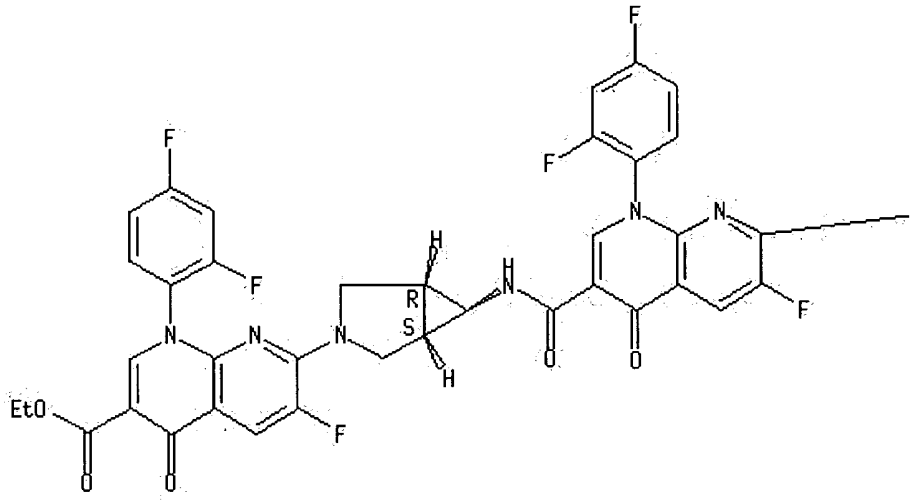
(purifn. of alatrofloxacin parenteral compns. and prepn. of alatrofloxacin oligomer as antibacterial agent)

RN 220293-27-6 HCAPLUS

CN L-Alaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[(1α,5α,6α)-3-[8-(2,4-difluorophenyl)-6-[[[(1α,5α,6α)-3-[8-(2,4-difluorophenyl)-6-(ethoxycarbonyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]amino]carbonyl]-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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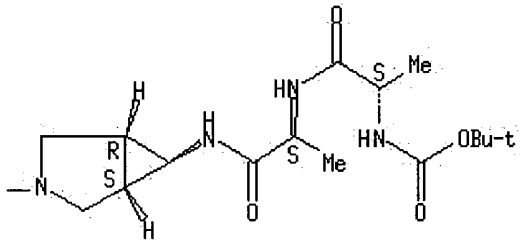

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1997:145237 HCAPLUS
DOCUMENT NUMBER: 126:157823
TITLE: Process for preparing azabicyclo naphthyridine carboxylic acid dipeptide prodrug
INVENTOR(S): Braish, Tamim F.; Castaldi, Michael J.; Watson, Harry A., Jr.
PATENT ASSIGNEE(S): Pfizer Inc., USA; Braish, Tamim F.; Castaldi, Michael J.; Watson, Harry A., Jr.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9700268 | A1 | 19970103 | WO 1996-IB257 | 19960327 |
| W: CA, JP, MX, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2224616 | AA | 19970103 | CA 1996-2224616 | 19960327 |
| EP 833837 | A1 | 19980408 | EP 1996-904996 | 19960327 |

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| EP 833837 | B1 | 20020731 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI | | | | | |
| JP 3029293 | B2 | 20000404 | JP 1997-502832 | 19960327 | |
| JP 10511983 | T2 | 19981117 | | | |
| AT 221544 | E | 20020815 | AT 1996-904996 | 19960327 | |
| PT 833837 | T | 20021129 | PT 1996-96904996 | 19960327 | |
| ES 2178701 | T3 | 20030101 | ES 1996-904996 | 19960327 | |
| US 5939550 | A | 19990817 | US 1998-981350 | 19980311 | |
| PRIORITY APPLN. INFO.: | | | US 1995-490827 | A1 19950615 | |
| | | | WO 1996-IB257 | W 19960327 | |

OTHER SOURCE(S): MARPAT 126:157823
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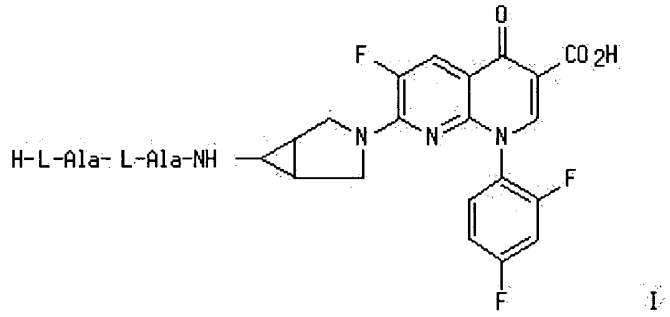



I

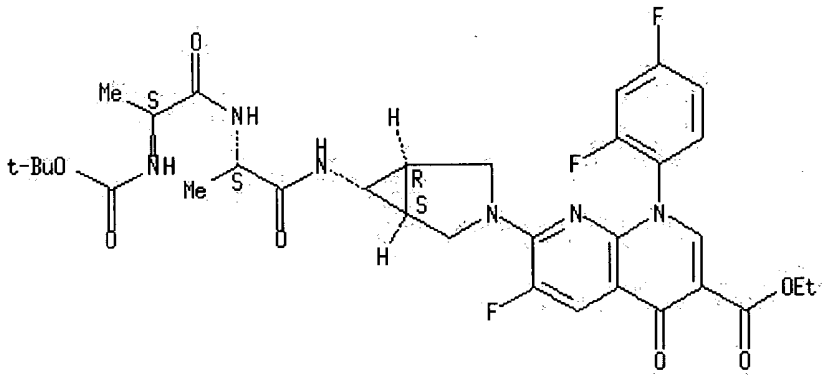
AB A process is given for prepg. a pharmaceutically acceptable acid addn. salt of prodrug acid I. Thus, N-Boc protected 7-[(1α, 5α, 6α)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid Et ester, Boc-Q-OEt, (Boc = tert-butoxycarbonyl) was deprotected by trifluoroacetic acid and the product coupled with Boc-Ala-Ala-OH using EEDQ and then treated with methanesulfonic acid to afford I mesylate. The latter prodrug serves as a water-sol. prodrug companion to known antibacterial agent H-Q-OH.

IT **186772-86-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn.of azabicyclo naphthyridine carboxylic acid dipeptide prodrug)

RN 186772-86-1 HCAPLUS

CN L-Alaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-alanyl-N-[(1α,5α,6α)-3-[8-(2,4-difluorophenyl)-6-(ethoxycarbonyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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FILE LAST UPDATED:  01 May 1997 (19970501/UP)

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  printed between 1907-1966 are available in the PAGE
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L9            2 S L8 AND L4

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L24          15 S L21 AND L15

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L30           5 S L29 AND HYDRO?
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L39            2 S L36 AND WINT, L?/AU
L40            0 S L39 NOT L38

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